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(54) Title: UREA DERIVATIVES

(57) Abstract: A medicament which contains a urea derivative or a salt thereof as an active ingredient is disclosed. The medicament has an excellent activity as VR1 antagonist and useful for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urge urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and/or inflammatory disorders.

UREA DERIVATIVES

DETAILED DESCRIPTION OF INVENTION

TECHNICAL FIELD

The present invention relates to a urea derivative which is useful as an active ingredient of pharmaceutical preparations. The urea derivative of the present invention has a vanilloid receptor (VR1) antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urge urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and/or inflammatory disorders.

BACKGROUND ART

Vanilloid compounds are characterized by the presence of vanillyl group or a functionally equivalent group. Examples of several vanilloid compounds or vanilloid receptor modulators are vanillin (4-hydroxy-3-methoxy-benzaldehyde), guaiacol (2-methoxy-phenol), zingerone (4-/4-hydroxy-3-methoxyphenyl/-2-butanon), eugenol-(2-methoxy4-/2-propenyl/phenol), and capsaicin (8-methy-N-vanillyl-6-nonene-amide).

Among others, capsaicin, the main pungent ingredient in "hot" chili peppers, is a specific neurotoxin that desensitizes C-fiber afferent neurons. Capsaicin interacts with vanilloid receptors (VR1), which are predominantly expressed in cell bodies of dorsal root ganglia (DRG) or nerve endings of afferent sensory fibers including C-fiber nerve endings [Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D: The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron. 21: 531-543, 1998]. The VR1

receptor was recently cloned [Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D: Nature 389: 816-824, (1997)] and identified as a nonselective cation channel with six transmembrane domains that is structurally related to the TRP (transient receptor potential) channel family. Binding of capsaicin to VR1 allows sodium, calcium and possibly potassium ions to flow down their concentration gradients, causing initial depolarization and release of neurotransmitters from the nerve terminals. VR1 can therefore be viewed as a molecular integrator of chemical and physical stimuli that elicit neuronal signals in a pathological conditions or diseases.

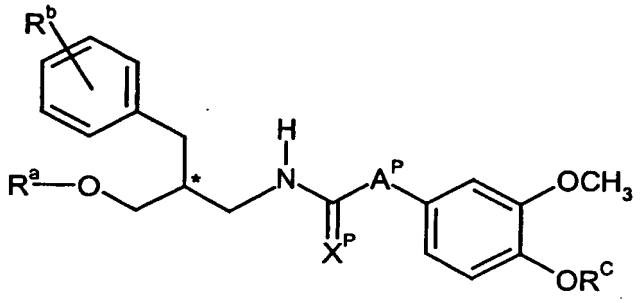
There are abundant of direct or indirect evidence that shows the relation between VR1 activity and diseases such as pain, ischaemia, and inflammatory (e.g., WO 99/00115 and 00/50387). Further, it has been demonstrated that VR1 transduce reflex signals that are involved in the overactive bladder of patients who have damaged or abnormal spinal reflex pathways [De Groat WC: A neurologic basis for the overactive bladder. Urology 50 (6A Suppl): 36-52, 1997]. Desensitisation of the afferent nerves by depleting neurotransmitters using VR1 agonists such as capsaicin has been shown to give promising results in the treatment of bladder dysfunction associated with spinal cord injury and multiple sclerosis [(Maggi CA: Therapeutic potential of capsaicin-like molecules - Studies in animals and humans. Life Sciences 51: 1777-1781, 1992) and (DeRidder D; Chandiramani V; Dasgupta P; VanPoppel H; Baert L; Fowler CJ: Intravesical capsaicin as a treatment for refractory detrusor hyperreflexia: A dual center study with long-term followup. J. Urol. 158: 2087-2092, 1997)].

It is anticipated that antagonism of the VR1 receptor would lead to the blockage of neurotransmitter release, resulting in prophylaxis and treatment of the condition and diseases associated with VR1 activity.

It is therefore expected that antagonists of the VR1 receptor can be used for prophylaxis and treatment of the condition and diseases including chronic pain,

neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence, inflammatory disorders, urge urinary incontinence (UUI), and/or overactive bladder.

WO 2000/50387 discloses the compounds having a vanilloid agonist activity represented by the general formula:



wherein;

X^P is an oxygen or sulfur atom;

A^P is $-NHCH_2-$ or $-CH_2-$;

R^a is a substituted or unsubstituted C_{1-4} alkyl group, or $R^{a1}CO-$;

wherein

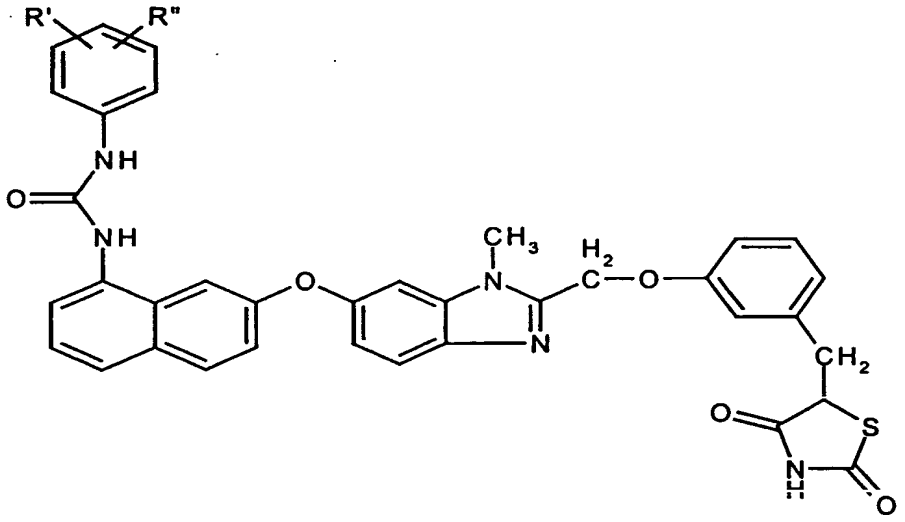
R^{a1} is an alkyl group having 1 to 18 carbon atoms, an alkenyl group having 2 to 18 carbon atoms, or substituted or unsubstituted aryl group having 6 to 10 carbon atoms;

R^b is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkoky group having 1 to 6 carbon atoms, a haloalkyl group having 1 to 6 carbon atoms or a halogen atom;

R^C is a hydrogen atom, an alkyl group having 1 to 4 carbon atom, an aminoalkyl, a diacid monoester or α-alkyl acid; and

the asteric mark * indicates a chiral carbon atom, and their pharmaceutically acceptable salts.

WO 2000/61581 discloses amine derivatives represented by the general formula:

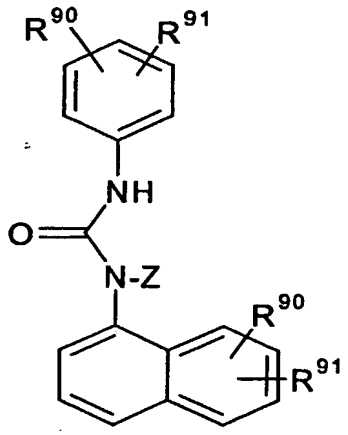


wherein

(R', R") represent (F, F), (CF_3, H), or (iPr, iPr)

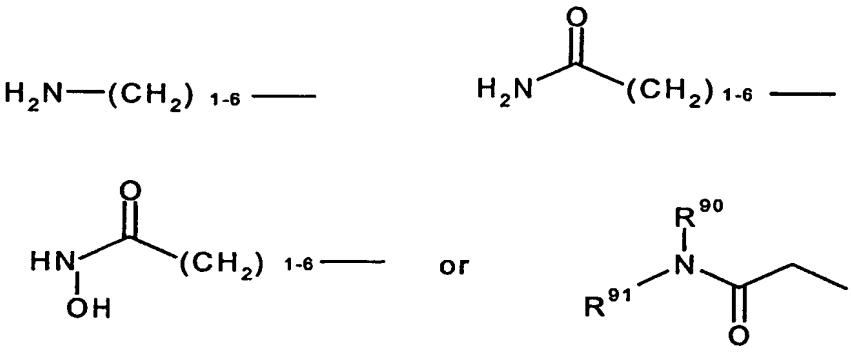
as useful agents for diabetes, hyperlipemia, arteriosclerosis and cancer.

WO 2000/75106 discloses the compounds represented by the general formula:



wherein

Z represents



in which

R^{90} is hydrogen, C_{1-12} alkyl, C_{3-8} cycloalkyl, or the like, and

R^{91} is amino-C_{1-6} alkyl, aminocarbonyl-C_{1-6} alkyl, or hydroxy-aminocarbonyl C_{1-6} alkyl; and

R^{90} and R^{91} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkoxy, fluoro, chloro, bromo, iodo, and nitro;

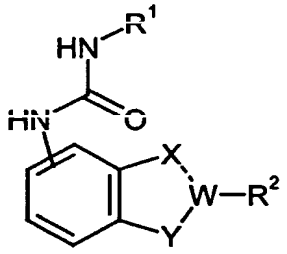
as useful agents for treating MMP-mediated diseases in mammals.

However, none of these reference discloses simple urea derivatives having pharmaceutical activity.

The development of a compound having effective VR1 antagonistic activity and the use of such compound for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urge urinary incontinence and/or overactive bladder have been desired.

SUMMARY OF THE INVENTION

This invention is to provide a medicament comprising an urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as an active ingredient:



(I)

wherein

R^1 is C_{1-6} alkyl substituted by phenyl or thienyl (in which said phenyl or thienyl are substituted by R^{11}, R^{12}, and R^{13}), C_{3-8} cycloalkyl optionally fused by benzene, thienyl, quinolyl, carbazolyl of which N-H is substituted by N-R^{11}, 1,2-oxazolyl substituted by R^{11}, naphthyl substituted by R^{14} and R^{15}, phenyl substituted by R^{11}, R^{12}, and R^{13}, phenyl fused by C_{4-8} cycloalkyl or saturated or unsaturatd C_{4-8} heterocyclic ring having one or two hetero atoms selected from the group consisting of N, O, S, and SO_2,

wherein said cycloalkyl and heterocyclic ring are optionally substituted by R^{11},

in which

R^{11}, R^{12} and R^{13} are different or identical and represent hydrogen, halogen, oxo, nitro, carboxyl, C_{1-6} alkyl optionally substituted by hydroxy or mono-, di-, or tri- halogen, carbamoyl, C_{1-6} alkylcarbamoyl, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri- halogen, C_{1-6} alkoxycarbonyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, morpholino, benzyl, phenoxy, mono-, di-, or tri- halogen substituted phenoxy, C_{1-6} alkylthio, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, C_{1-6} alkyl substituted 4,5-dihydro-1,3-oxazolyl, 1,2,3-thiadiazolyl, phenyl optionally substituted by one to three substituents,

in which the substituents are each different or identical and selected from the group consisting of hydrogen, halogen, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkanoyl, and carboxy, or

the substituent represented by the formula $-SO_2-N-R^{111}$

wherein

R^{111} represents hydrogen, 5-methyl-isoxazole, or 2,4 dimethylpyrimidine;

R^{14} is hydrogen, hydroxy, or C_{1-6} alkoxy;

R^{15} is hydrogen, hydroxy, or C_{1-6} alkoxy;

X, Y, and W are different or identical represent C, CH, CH_2, C(O), N, NH, S, O, SO or SO_2;

the dashed line between X and W represents a single bond or a double bond;

R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, mercapto, trifluoromethyl, and methylthio,
or
is absent;

with the proviso that if the bond between X--W is a double,

X is N or CH;

W is N or C; and

Y is selected from the group consisting of NH, S, O, CH_2, SO, and SO_2;

with the proviso that when W is N, R^2 is absent;

if the bond between X--W is a single,

X and Y independently represent CH_2, CO, NH, S, O, SO, or SO_2; and

W is N, CH, S, O, SO or SO_2;

with the proviso that when W is S, O, SO or SO_2, R^2 is absent.

The urea derivative of formula (I), its tautomeric and stereoisomeric form, and salts thereof surprisingly shows excellent VR1 antagonistic activity. They are, therefore, suitable especially for the prophylaxis and treatment of diseases associated with VR1

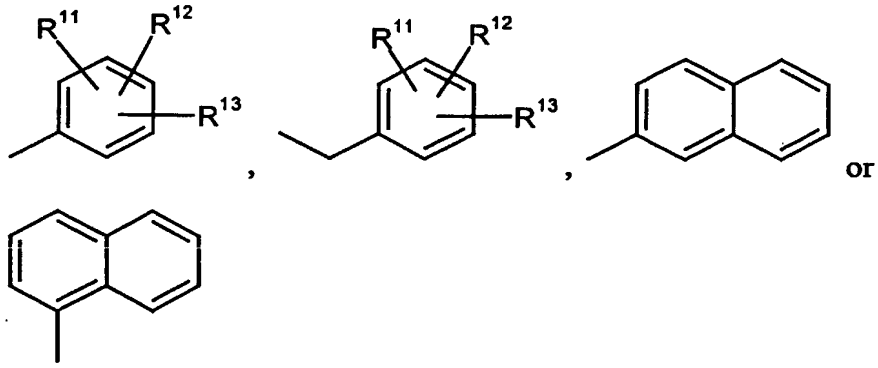
activity, in particular for the treatment of urge urinary incontinence and/or overactive bladder.

This invention is also to provide a method for treating or preventing a disorder or disease associated with VR1 activity in a human or animal subject, comprising administering to said subject a therapeutically effective amount of the urea derivative shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof.

Further this invention is to provide a use of the urea derivative shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof in the preparation of a medicament. Preferably, said medicament is suitable for treating or preventing a disorder or disease associated with VR1 activity.

In another preferable embodiment, the urea derivative of formula (I) are those wherein;

R^1 is



wherein

R^{11}, R^{12}, and R^{13} are different or identical and represent hydrogen, halogen, nitro, carboxyl, C_{1-6} alkyl optionally substituted by hydroxy or mono-, di-, or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri- halogen, C_{1-6} alkoxycarbonyl, carbamoyl, C_{1-6} alkylcarbamoyl, amino, C_{1-6} alkylamino,

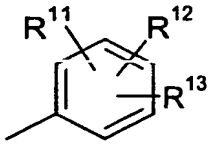
di(C_{1-6} alkyl)amino, morpholino, phenyl, benzyl, phenoxy, mono-, di-, or tri- halogen substituted phenoxy, mono-, di-, or tri- halogen substituted phenyl, C_{1-6} alkylthio, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, or the substituent represented by the formula $-SO_2-N-R^{111}$

wherein

R^{111} is hydrogen, 5-methyl-isoxazole, or 2,4-dimethyl-pyrimidine.

In another preferable embodiment, the urea derivative of formula (I) are those wherein;

R^1 is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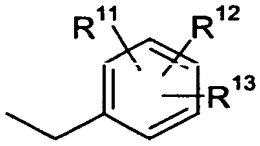
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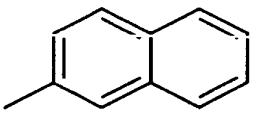
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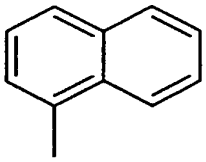
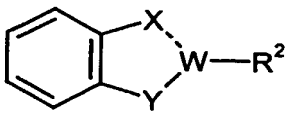


R^{11}, R^{12}, and R^{13} are different or identical and represent hydrogen, fluoro, chloro, bromo, methyl, isopropyl, methoxy, nitro, ethoxy-carbonyl, phenyl, phenoxy, 4-chlorophenyl, methylthio, acetyl, or trifluoromethyl.

In another preferable embodiment, the urea derivative of formula (I) are those wherein;



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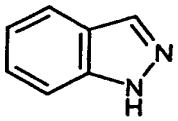
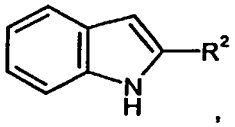
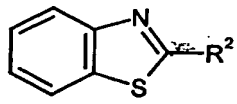
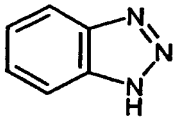
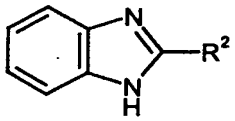
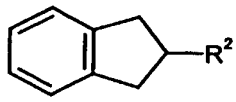
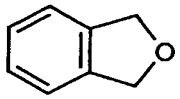
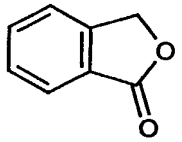
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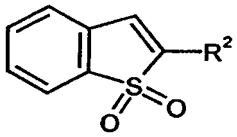


wherein

R^2 is hydrogen, methyl, hydroxy, mercapto, trifluoromethyl, or methylthio.

Most preferably, said urea derivative of the formula (I) is selected from the group consisting of:

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(1H-indazol-5-yl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(1H-indol-7-yl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(1H-indol-4-yl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-[2-(trifluoromethyl)-1H-benzimidazol-4-yl]urea;
N-(4-bromobenzyl)-N'-(1H-indol-7-yl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(1,1-dioxido-1-benzothien-6-yl)urea;

N-(1,3-benzothiazol-6-yl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;
N-(2-methyl-1,3-benzothiazol-5-yl)-N'-(3-methylphenyl)urea;
N-(4-fluorophenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;
N-(2-methyl-1,3-benzothiazol-5-yl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(2-methyl-1,3-benzothiazol-5-yl)-N'-(4-phenoxyphenyl)urea;
N-(4-bromophenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;
N-(2-methyl-1,3-benzothiazol-5-yl)-N'-(2-naphthyl)urea;
N-(3,4-dichlorophenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;
N-(2,4-difluorophenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;
N-(3-chloro-4-methylphenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;
N-[2-chloro-5-(trifluoromethyl)phenyl]-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;
N-(4-isopropylphenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;
N-(2-methyl-1,3-benzothiazol-5-yl)-N'-(1-naphthyl)urea;
N-(1H-indol-4-yl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(1,1'-biphenyl-3-yl)-N'-(1H-indol-4-yl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(2-methyl-1H-benzimidazol-4-yl)urea;
N-(2-methyl-1H-benzimidazol-4-yl)-N'-(4-phenoxyphenyl)urea;
N-(1H-indol-4-yl)-N'-(1-naphthyl)urea;
N-(3,4-dichlorophenyl)-N'-(1H-indol-4-yl)urea;
N-(3-chloro-4-methylphenyl)-N'-(1H-indol-4-yl)urea;
N-(1H-indol-4-yl)-N'-(4-isopropylphenyl)urea;
N-(4-fluorophenyl)-N'-(1H-indazol-5-yl)urea;
N-[2-chloro-5-(trifluoromethyl)phenyl]-N'-(1H-indol-4-yl)urea;
ethyl 3-{[(1H-indol-4-ylamino)carbonyl]amino}benzoate;
and
N-(4-bromobenzyl)-N'-(1H-indol-4-yl)urea.

Preferably, the medicament of the present invention further comprise one or more pharmaceutically acceptable excipients.

The medicament having at least one urea derivative of the formula (I), its tautomeric and stereoisomeric form, and salts thereof is effective for treating or preventing a disease selected from the group consisting of urge urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration and/or stroke, since the diseases also relate to VR1 activity.

Alkyl per se and "alk" and "alkyl" in alkoxy, alkanoyl, alkylthio, alkylamino, alkylaminocarbonyl, alkylaminosulphonyl, alkylsulphonylamino, alkoxycarbonyl, alkoxycarbonylamino, alkylcarbamoyl and alkanoylamino represent a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkanoyl illustratively and preferably represents acetyl and propanoyl.

Alkylamino represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino and N-n-hexyl-N-methylamino.

Alkylaminocarbonyl or alkylcarbamoyl represents an alkylaminocarbonyl radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminocarbonyl, ethylaminocarbonyl, n-propylamino-carbonyl, isopropylamino-carbonyl, tert-butylaminocarbonyl, n-pentylamino-carbonyl, n-hexylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-diethylamino-

carbonyl, N-ethyl-N-methylaminocarbonyl, N-methyl-N-n-propylaminocarbonyl, N-isopropyl-N-n-propylaminocarbonyl, N-t-butyl-N-methylaminocarbonyl, N-ethyl-N-n-pentylamino-carbonyl and N-n-hexyl-N-methylaminocarbonyl.

Alkoxycarbonyl illustratively and preferably represents methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl. Alkoxycarbonylamino illustratively and preferably represents methoxycarbonylamino, ethoxycarbonylamino, n-propoxycarbonylamino, isopropoxycarbonylamino, tert-butoxycarbonylamino, n-pentoxycarbonylamino and n-hexoxycarbonylamino.

Alkanoylamino illustratively and preferably represents acetylamino and ethylcarbonylamino.

Halogen represents fluorine, chlorine, bromine and iodine.

Aryl per se and in arylamino and in arylcarbonyl represents a mono- to tricyclic aromatic carbocyclic radical having generally 6 to 14 carbon atoms, and more preferably from 6-10 carbon atoms, optionally substituted with one or more substituents. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, biphenyl, fluorenonyl and the like.

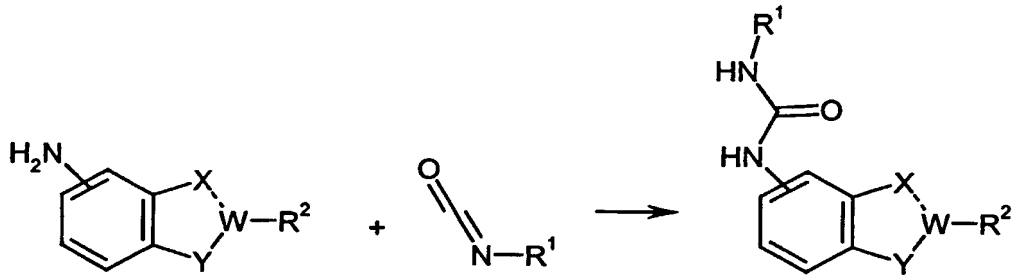
Heterocyclic ring refers to a 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. The heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring and may be partially or fully saturated or aromatic. Examples of such rings include, but are not limited to thienyl, benzothienyl, furanyl, benzofuranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, isothiazolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, imidazolyl, thiadiazolyl, benzothiadiazolyl,

oxadiazolyl, benzothiazolyl, indolyl, carbazolyl, quinolinyl, isoquinolinyl, benzodioxolyl, indazolyl, indazolinolyl and the like

EMBODIMENT OF THE INVENTION

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by either of the methods [A], [B] and [C] below. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis (3rd Edition)" by Greene and Wuts, John Wiley and Sons, New York 1999.

[Method A]



[II] [III] [I]

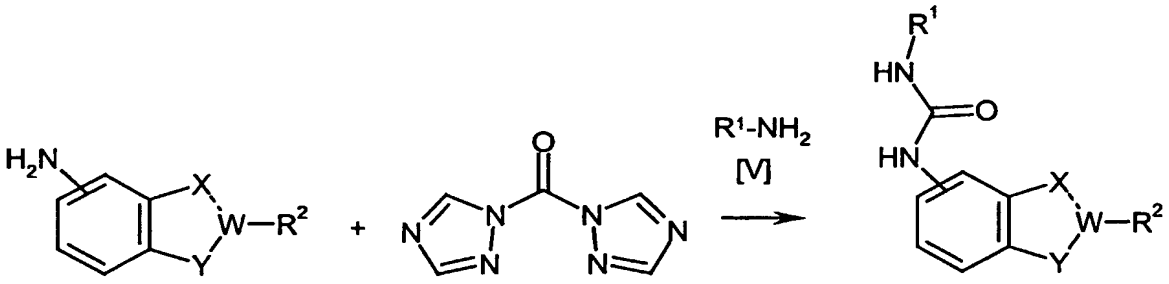
The compound [I] wherein R^1, R^2, X, Y, and W are the same as defined above, can be prepared by the reaction of an amine derivative formula [II] (wherein R^2, X, Y, and W are the same as defined above)and isocyanate of the formula [III] (wherein R^1 is the same as defined above).

The reaction may be carried out in a solvent including, for instance, ethers, such as dioxane, and tetrahydrofuran; aromatic hydrocarbons such as benzene, toluene and

xylene; nitriles such as acetonitrile; amides such as dimethylformamide (DMF) and dimethylacetamide; sulfoxides such as dimethyl sulfoxide, and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 30°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

[Method B]



[II] [IV] [I]

Alternatively, the compound[I] wherein R^1, R^2, X, Y and W are the same as defined above, can also be prepared by (1) reacting a amine derivative formula [II] (wherein R^2, X, Y, and W are the same as defined above)and 1,1'-carbonyldi(1,2,4-triazole) (CDT)[IV], and (2) adding amine represented by the formula R^1-NH_2 [V](wherein R^1 is the same as defined above) to the reaction mixture. The reaction (1) may be carried out in a solvent including, for instance, ethers, such as dioxane, and tetrahydrofuran; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as dimethylformamide (DMF) and dimethylacetamide; sulfoxides such as dimethyl sulfoxide, and others.

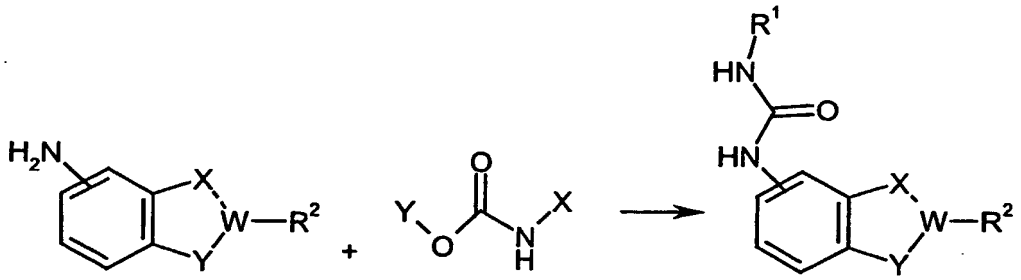
The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 50°C.

The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

The reaction (2) may be carried out in a solvent including, for instance, ethers, such as dioxane, and tetrahydrofuran; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as dimethylformamide (DMF) and dimethylacetamide; sulfoxides such as dimethyl sulfoxide, and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 30°C to 100°C. The reaction may be conducted for, usually, 1 hour to 48 hours and preferably 2 to 24 hours.

[Method C]



[II] [VI] [I]

Alternatively, the compound [I] (wherein R^1, R^2, X, Y, and W are the same as defined above) can be prepared by reacting an amine derivative formula [II] (wherein R^2, X, Y, and W are the same as defined above)and carbamate of the formula [VI] (wherein X is the same as defined above and Y represents phenyl).

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene;

nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone(NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 40 hours and preferably 1 to 24 hours.

The amine derivatives formula [II], Isocyanates [III], CDT [IV], amines [V], and carbamates [VI] are commercially available or can be prepared by the use of known techniques or by method described in the examples.

When the compound shown by the formula (I) or a salt thereof has tautomeric isomers and/or stereoisomers (e.g., geometrical isomers and conformational isomers), each of their separated isomer and mixtures are also included in the scope of the present invention.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid,

methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of

metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation, carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients therefore. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar, bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose,

corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be

varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg /kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven advantageous to administer quantities of about 0.001 to 100 mg /kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

EXAMPLES

The present invention will be described as a form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

Mass spectra were obtained using electrospray (ES) ionization techniques (micromass Platform LC). Melting points are uncorrected. Liquid Chromatography - Mass spectroscopy (LC-MS) data were recorded on a Micromass Platform LC with Shimadzu Phenomenex ODS column(4.6 mm X 30 mm) flushing a mixture of acetonitrile-water (9:1 to 1:9) at 1 ml/min of the flow rate. TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150 μm)) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Tokyo kasei kogyo co. Ltd., Arch cooporation.

All starting materials are commercially available or can be prepared using methods cited in the literature.

The effect of the present compounds were examined by the following assays and pharmacological tests.

[Measurement of capsaicin-induced Ca^{2+} influx in the human VR1-transfected CHO cell line] (Assay 1)

(1) Establishment of the human VR1-CHOluc9aeq cell line

Human vanilloid receptor (hVR1) cDNA was cloned from libraries of axotomized dorsal root ganglia (WO2000/29577). The cloned hVR1 cDNA

was constructed with pcDNA3 vector and transfected into a CHOluc9aeq cell line. The cell line contains aequorin and CRE-luciferase reporter genes as read-out signals. The transfectants were cloned by limiting dilution in selection medium (DMEM/F12 medium (Gibco BRL) supplemented with 10% FCS, 1.4 mM Sodium pyruvate, 20 mM HEPES, 0.15% Sodium bicarbonate, 100 U/ml penicillin, 100 µg/ml streptomycin, 2 mM glutamine, non-essential amino acids and 2 mg/ml G418). Ca^{2+} influx was examined in the capsaicin-stimulated clones. A high responder clone was selected and used for further experiments in the project. The human VR1-CHOluc9aeq cells were maintained in the selection medium and passaged every 3-4 days at 1-2.5x10^5 cells/flask (75 mm^2).

(2) Measurement of Ca^{2+} influx using FDSS-3000

Human VR1-CHOluc9aeq cells were suspended in a culture medium which is the same as the selection medium except for G418 and seeded at a density of 1,000 cells per well into 384-well plates (black walled clear-base / Naige Nunc International). Following the culture for 48 hrs the medium was changed to 2 µM Fluo-3 AM (Molecular Probes) and 0.02% Puronic F-127 in assay buffer (Hank's balanced salt solution (HBSS), 17 mM HEPES (pH7.4), 1 mM Probenecid, 0.1% BSA) and the cells were incubated for 60 min at 25°C. After washing twice with assay buffer the cells were incubated with a test compound or vehicle for 20 min at 25°C. Mobilization of cytoplasmic Ca^{2+} was measured by FDSS-3000 (λ_{ex}=488nm, λ_{em}=540nm / Hamamatsu Photonics) for 60 sec after the stimulation with 10 nM capsaicin. Integral R was calculated and compared with controls.

[Measurement of the capsaicin-induced Ca^{2+} influx in primary cultured rat dorsal root ganglia neurons] (Assay 2)

(1) Preparation of rat dorsal root ganglia neurons

New born Wister rats (5-11 days) were sacrificed and dorsal root ganglia (DRG) was removed. DRG was incubated with 0.1% trypsin (Gibco BRL) in PBS(-) (Gibco BRL) for 30 min at 37°C, then a half volume of fetal calf serum (FCS) was added and the cells were spun down. The DRG neuron cells were resuspended in Ham F12/5% FCS/5% horse serum (Gibco BRL) and dispersed by repeated pipetting and passing through 70 μm mesh (Falcon). The culture plate was incubated for 3 hours at 37°C to remove contaminating Schwann cells. Non-adherent cells were recovered and further cultured in laminin-coated 384 well plates (Nunc) at $1x10^4$ cells/50 μl/well for 2 days in the presence of 50 ng/ml recombinant rat NGF (Sigma) and 50 μM 5-fluorodeoxyuridine (Sigma).

(2) Ca^{2+} mobilization assay

DRG neuron cells were washed twice with HBSS supplemented with 17 mM HEPES (pH 7.4) and 0.1% BSA. After incubating with 2 μM fluo-3AM (Molecular Probe), 0.02% PF127 (Gibco BRL) and 1 mM probenecid (Sigma) for 40 min at 37°C, cells were washed 3 times. The cells were incubated with VR1 antagonists or vehicle (dimethylsulphoxide) and then with 1 μM capsaicin in FDSS-6000 (λ_{ex}=480nm, λ_{em}=520nm / Hamamatsu Photonics). The fluorescence changes at 480nm were monitored for 2.5 min. Integral R was calculated and compared with controls.

[Organ bath assay to measure the capsaicin-induced bladder contraction] (Assay 3)

Male Wistar rats (10 week old) were anesthetized with ether and sacrificed by dislocating the necks. The whole urinary bladder was excised and placed in oxygenated Modified Krebs-Henseleit solution (pH 7.4) of the following composition (112mM NaCl, 5.9mM KCl, 1.2mM $MgCl_2$, 1.2mM NaH_2PO_4, 2mM $CaCl_2$, 2.5mM $NaHCO_3$, 12mM glucose). Contractile responses of the urinary bladder were studied as described previously [Maggi CA et al: Br.J.Pharmacol. 108: 801-805, 1993]. Isometric tension was recorded under a load of 1 g using longitudinal strips of rat detrusor muscle. Bladder strips were equilibrated for 60 min before each stimulation. Contractile response to 80 mM KCl was determined at 15 min intervals until reproducible responses were obtained. The response to KCl was used as an internal standard to evaluate the maximal response to capsaicin. The effects of the compounds were investigated by incubating the strips with compounds for 30 min prior to the stimulation with 1 μM capsaicin (vehicle: 80% saline, 10% EtOH, and 10% Tween 80). One of the preparations made from the same animal was served as a control while the others were used for evaluating compounds. Ratio of each capsaicin-induced contraction to the internal standard (i.e. KCl-induced contraction) was calculated and the effects of the test compounds on the capsaicin-induced contraction were evaluated.

[Measurement of Ca^{2+} influx in the human P2X1-transfected CHO cell line]

(1) Preparation of the human P2X1-transfected CHOluc9aeq cell line

Human P2X1-transfected CHOluc9aeq cell line was established and maintained in Dulbecco's modified Eagle's medium (DMEM/F12) supplemented with 7.5% FCS, 20 mM HEPES-KOH (pH 7.4), 1.4 mM sodium pyruvate, 100 U/ml penicillin, 100 μg/ml streptomycin, 2 mM glutamine (Gibco BRL) and 0.5 Units/ml apyrase (grade I, Sigma). The suspended cells were seeded in each well of 384-well optical bottom black

plates (Nalge Nunc International) at 3 x 10^3 / 50 µl / well. The cells were cultured for following 48 hrs to adhere to the plates.

(2) Measurement of the intracellular Ca^{2+} levels

P2X1 receptor agonist-mediated increases in cytosolic Ca^{2+} levels were measured using a fluorescent Ca^{2+} chelating dye, Fluo-3 AM (Molecular Probes). The plate-attached cells were washed twice with washing buffer (HBSS, 17 mM HEPES-KOH (pH 7.4), 0.1% BSA and 0.5 units/ml apyrase), and incubated in 40 µl of loading buffer (1 µM Fluo-3 AM, 1 mM probenecid, 1 µM cyclosporin A, 0.01% pluronic (Molecular Probes)in washing buffer) for 1 hour in a dark place. The plates were washed twice with 40 µl washing buffer and 35 µl of washing buffer were added in each well with 5 µl of test compounds or *2',3'-o*-(2,4,6-trinitrophenyl) adenosine 5'-triphosphate (Molecular Probes) as a reference. After further incubation for 10 minutes in dark 200 nM α,β-methylene ATP agonist was added to initiate the Ca^{2+} mobilization. Fluorescence intensity was measured by FDSS-6000 (λ_{ex}=410nm, λ_{em}=510nm / Hamamatsu Photonics) at 250 msec intervals. Integral ratios were calculated from the data and compared with that of a control.

[Measurement of capsaicin-induced bladder contraction in anesthetized rats] (Assay 4)

(1) Animals

Female Sprague-Dawley rats (200~250 g / Charles River Japan) were used.

(2) Catheter implantation

Rats were anesthetized by intraperitoneal administration of urethane (Sigma) at 1.2 g/kg. The abdomen was opened through a midline incision, and a polyethylene catheter (BECTON DICKINSON, PE50) was implanted into the bladder through the dome. In parallel, the inguinal region was incised, and a polyethylene catheter (Hibiki, size 5) filled with 2 IU / ml of heparin (Novo Heparin, Aventis Pharma) in saline (Otsuka) was inserted into a common iliac artery.

(3) Cystometric investigation

The bladder catheter was connected via T-tube to a pressure transducer (Viggo-Spectramed Pte Ltd, DT-XXAD) and a microinjection pump (TERUMO). Saline was infused at room temperature into the bladder at a rate of 2.4 ml/hr. Intravesical pressure was recorded continuously on a chart pen recorder (Yokogawa). At least three reproducible micturition cycles, corresponding to a 20-minute period, were recorded before a test compound administration and used as baseline values.

(4) Administration of test compounds and stimulation of bladder with capsaicin

The saline infusion was stopped before administrating compounds. A testing compound dissolved in the mixture of ethanol, Tween 80 (ICN Biomedicals Inc.) and saline (1 : 1 : 8, v/v/v) was administered intraarterially at 10 mg/kg. 2 min after the administration of the compound 10 μg of capsaicin (Nacalai Tesque) dissolved in ethanol was administered intraarterially.

(5) Analysis of cystometry parameters

Relative increases in the capsaicin-induced intravesical pressure were analyzed from the cystometry data. The capsaicin-induced bladder pressures were compared with the maximum bladder pressure during micturition

without the capsaicin stimulation. The testing compounds–mediated inhibition of the increased bladder pressures was evaluated using Student's t-test. A probability level less than 5% was accepted as significant difference.

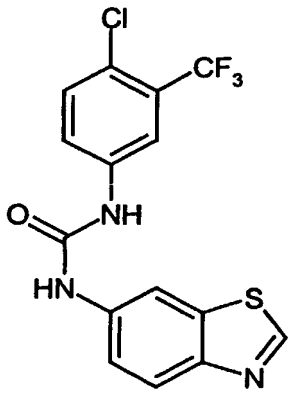
Results of IC_{50} of capsaicin-induced Ca^{2+} influx in the human VR1-transfected CHO cell line are shown in Examples and tables of the Examples below. The data corresponds to the compounds as yielded by solid phase synthesis and thus to levels of purity of about 40 to 90%. For practical reasons, the compounds are grouped in four classes of activity as follows:

$$IC_{50} = A \quad 0.1\,\mu M < B \quad 0.5\,\mu M < C \quad 1\,\mu M < D$$

The compounds of the present invention also show excellent selectivity, and strong activity in other assays (2)-(4) described above.

Example 1

N-(1,3-benzothiazol-6-yl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea



This example was performed according to the general method A.

To a stirred solution of 1,3-benzothiazol-6-amine (50.0 mg, 0.33 mmol) in 1,4-dioxane (5.0 ml) was added a solution of 1-chloro-4-isocyanato-2-(trifluoromethyl)-

benzene (88.5 mg, 0.40 mmol) in 1,4-dioxane (1.0 ml) at room temperature. A catalytic amount (2 drops) of pyridine was added and the reaction mixture was warmed to 50°C, and stirred for 20 hrs at the same temperature. The solvent was removed under reduced pressure, and the residue was washed with $^{i}Pr_2O$/MeOH to give N-(1,3-benzothiazol-6-yl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea as a grayish powder:

mp 225-228°C;

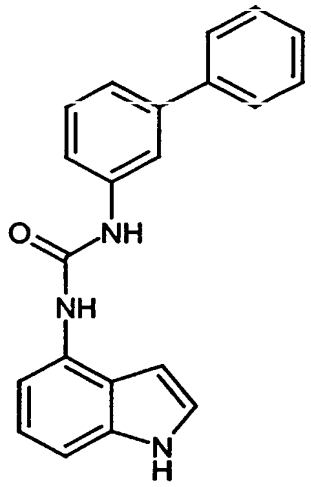
Molecular weight 371.77

MS (M+H):372

Activity grade:A

Example 2

N-(1,1'-biphenyl-3-yl)-N'-(1H-indol-4-yl)urea



This example was performed according to the general method B.

To a suspension of 1,1'-carbonyldi(1,2,4-triazole) (62.1 mg, 0.38 mmol) in THF (5.0 ml), was added dropwise a solution of 1H-indol-4-amine (50.0 mg, 0.38 mmol) in THF (1.0ml) at room temperature. The resulting suspension was stirred for 1hour.

1,1'-biphenyl-3-amine (64.0mg, 0.4mmol) was added to the suspension at room temperature. The reaction mixture was stirred at 50°C for 15hrs. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in a mixture of ethyl acetate and ethanol (1:1), and was passed through a silicagel short cartridge (1g Si / 6ml). The cartridge was washed with a mixture of ethyl acetate and ethanol (1:1). The combined filtrates were concentrated to give a solid.

The crude product was washed with a mixture of isopropanol and isopropyl ether to give N-(1,1'-biphenyl-3-yl)-N'-(1H-indol-4-yl)urea as a powder (59.0mg, 48%).

m.p. 213-215°C;
Molecular weight 327.39
MS (M+H):328
Activity grade:A

According to procedures similar to the examples above, the following compounds were synthesized and tested. The compounds listed below can be prepared by either of the methods A, B or C.

Table 1

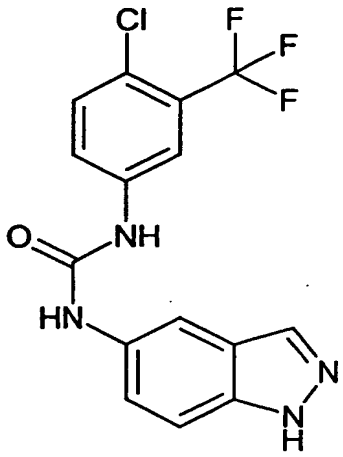
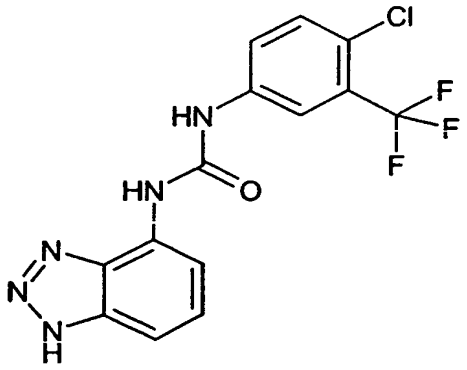
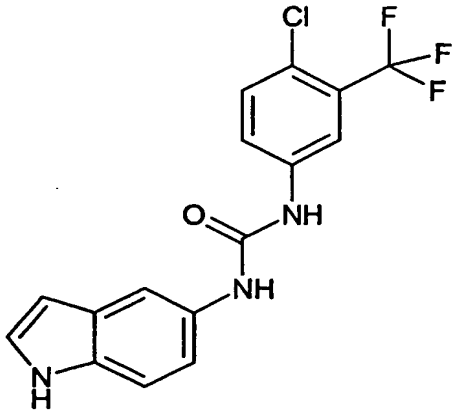
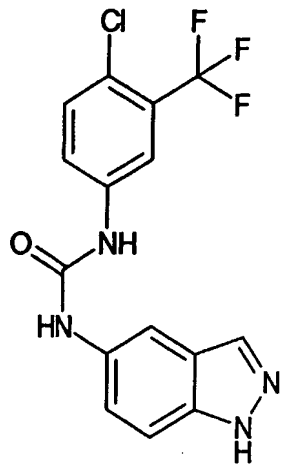
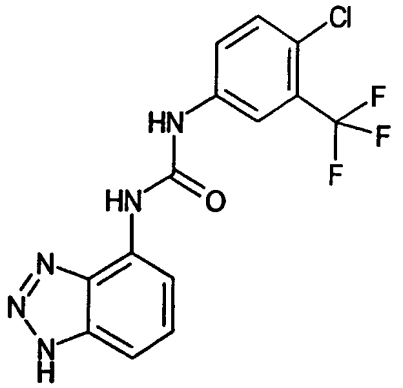
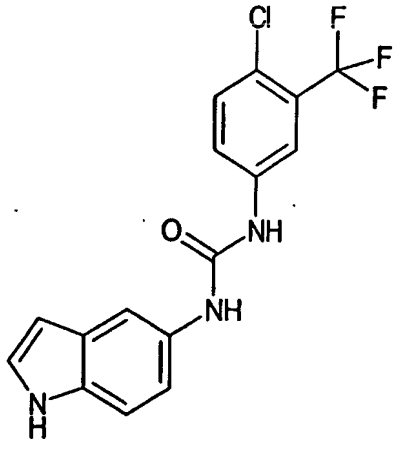
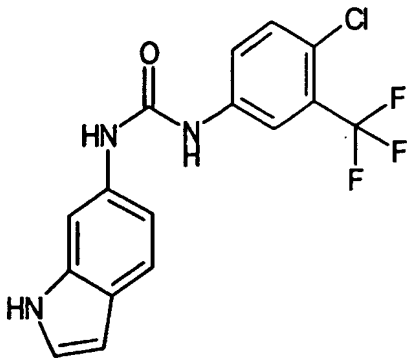
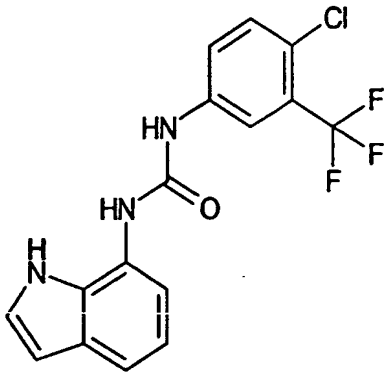
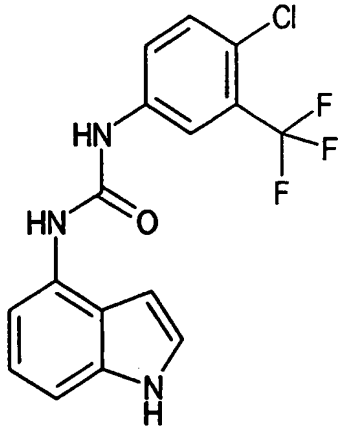
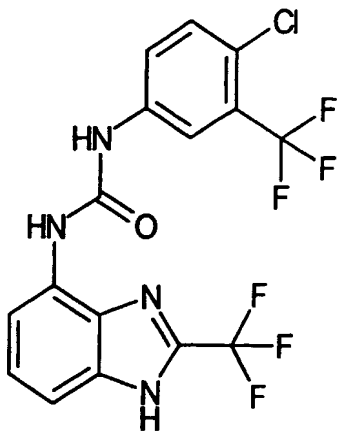
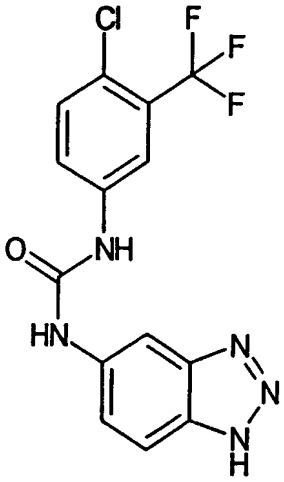
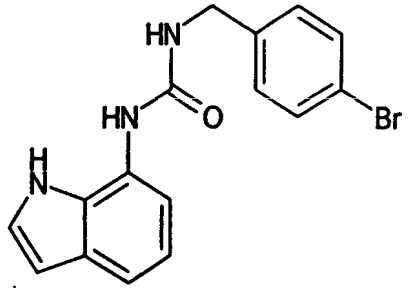
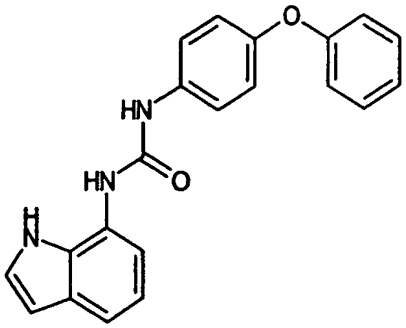
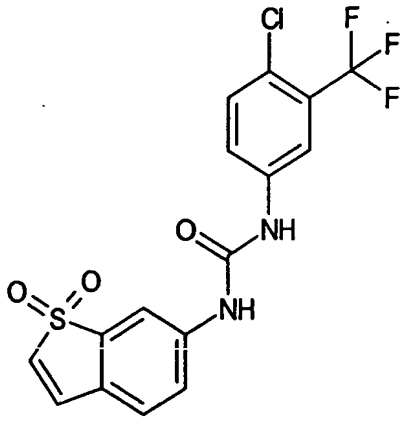
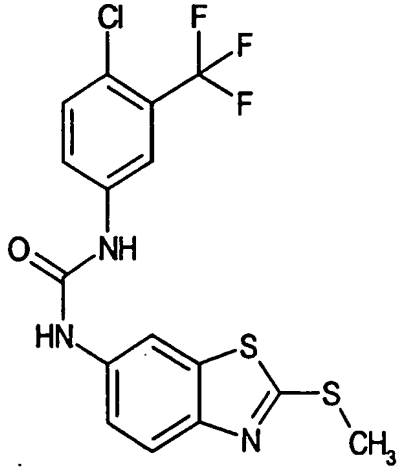
Ex. NO.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
3		354.7214	355	>250	A
4		355.7089	356	232-235	B
5		353.7338	354	234-235	B

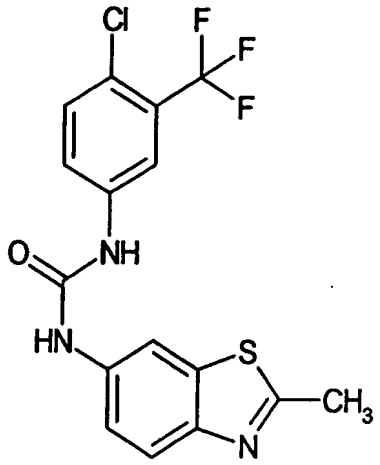
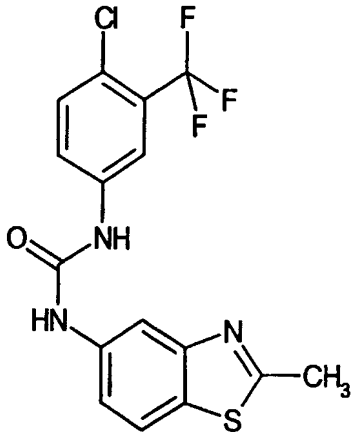
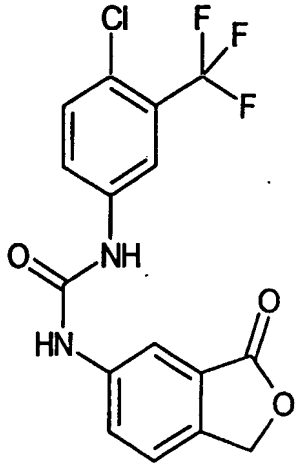
Table 1

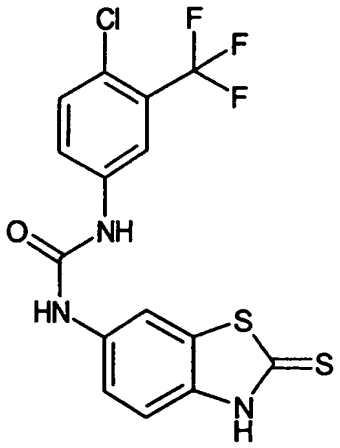
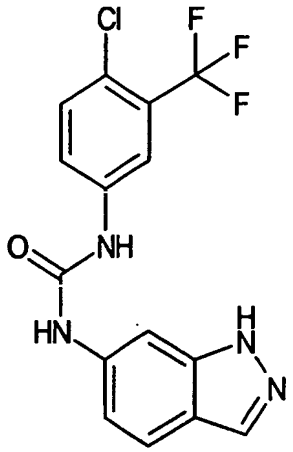
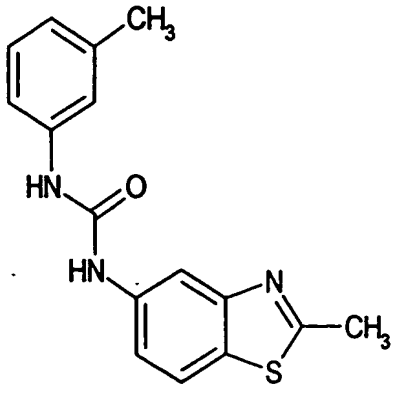
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
3		354,72135	355	>250	A
4		355,70893	356	232-235	B
5		353,73377	354	234-235	B

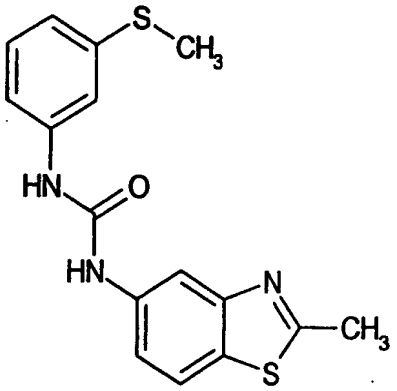
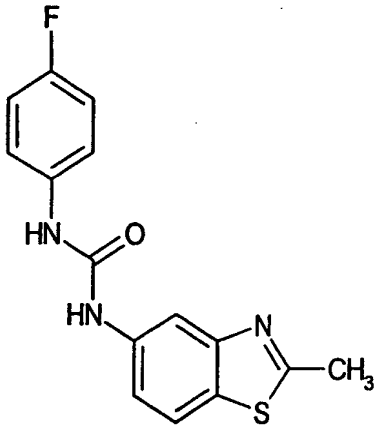
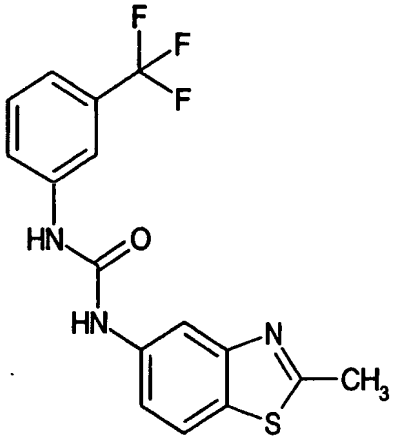
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
6		353,73377	354	245-248	B
7		353,73377	354	229-233	A
8		353,73377	354	230-233	A

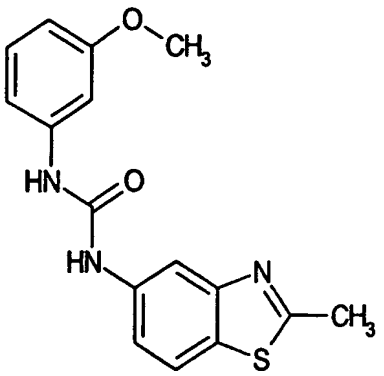
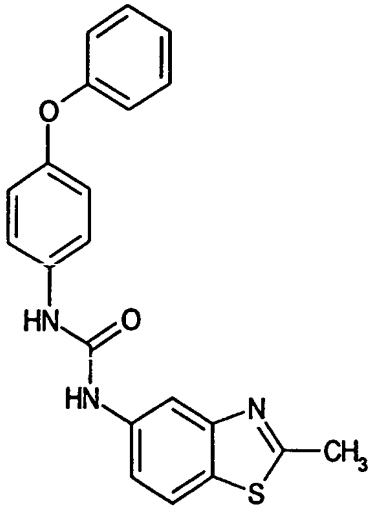
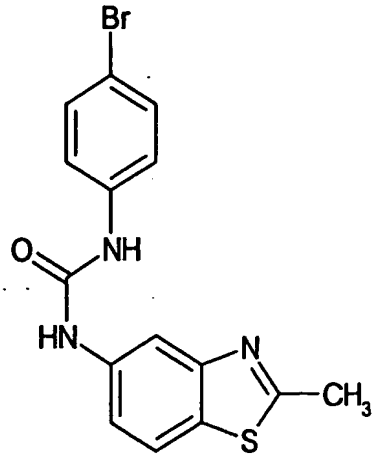
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
9		422,71973	423	165-169	A
10		355,70893	356	>250	B
11		344,21348	344	205-208	A

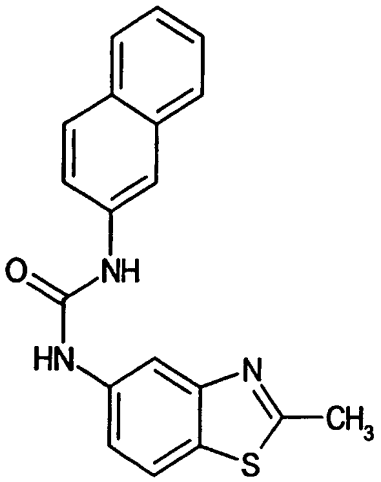
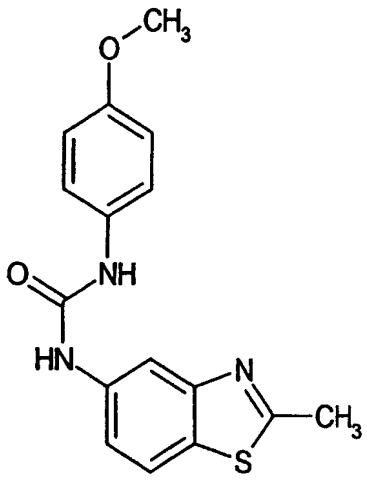
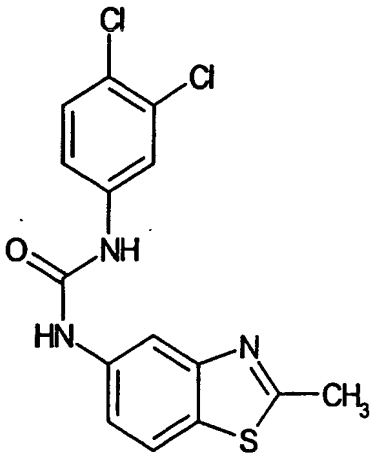
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
12		343,38854	344	216-218	B
13		402,7819	403	ND	A
14		417,86177	418	236-238	B

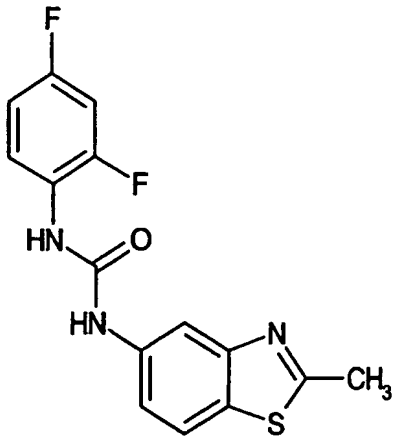
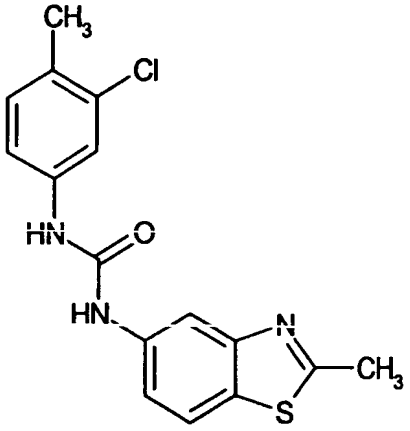
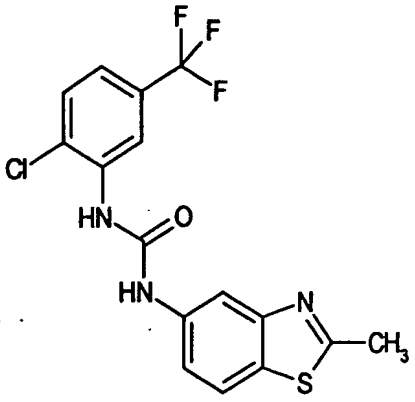
Ex. No	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
15		385,79777	386	234-235	B
16		385,79777	386	152-155	A
17		370,7179	371	>250	B

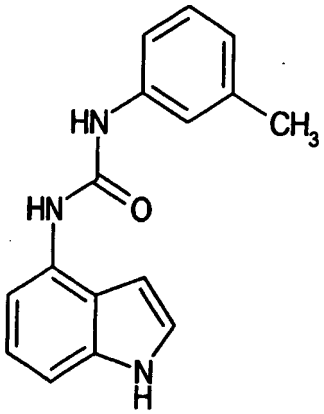
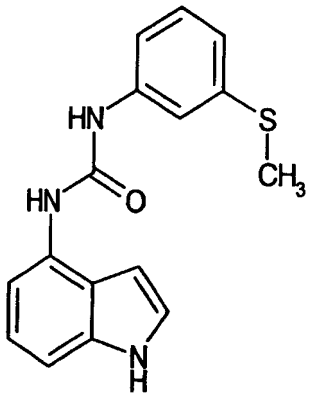
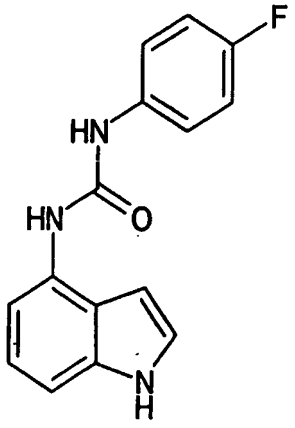
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
18		403,83468	404	>250	C
19		354,72135	355	>250	C
20		297,38145	298	200-202	A

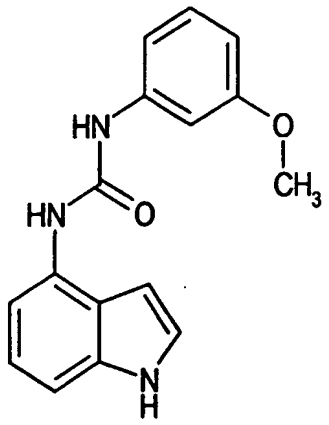
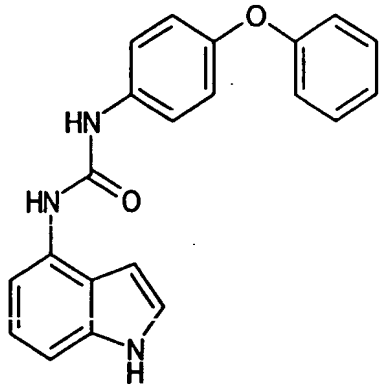
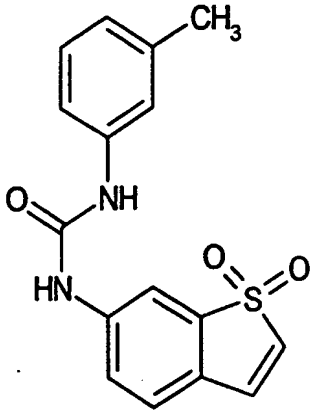
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
21		329,44545	330	225-227	B
22		301,34479	302	241-242	A
23		351,35274	352	229-231	A

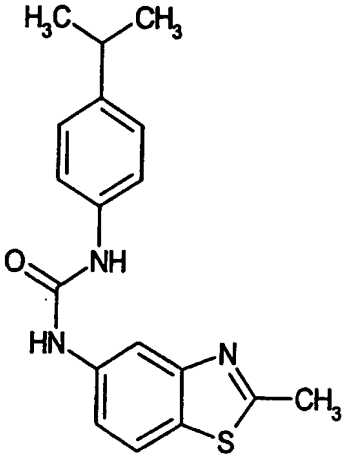
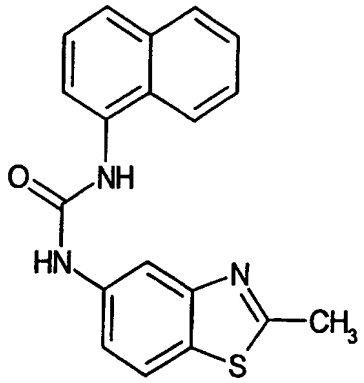
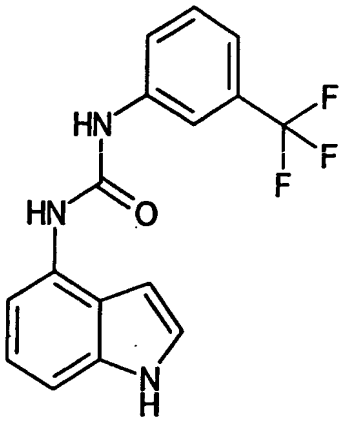
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
24		313,38085	314	199-201	B
25		375,45254	376	228-229	A
26		362,25039	364	>250	A

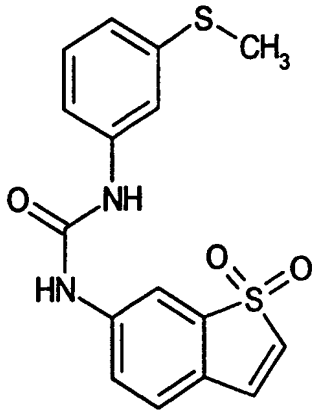
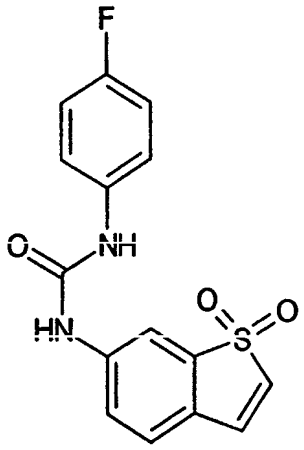
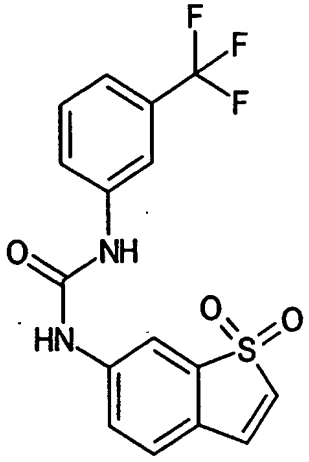
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
27		333,4149	334	>250	A
28		313,38085	314	215-217	B
29		352,24442	352	231-233	A

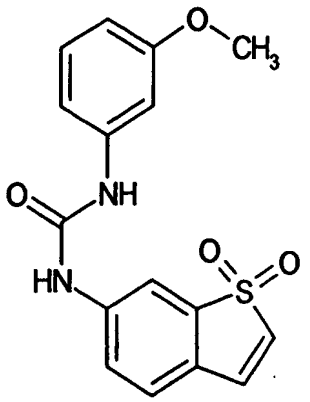
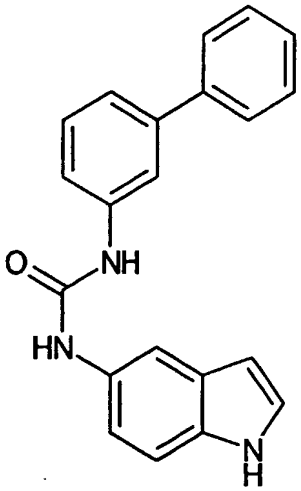
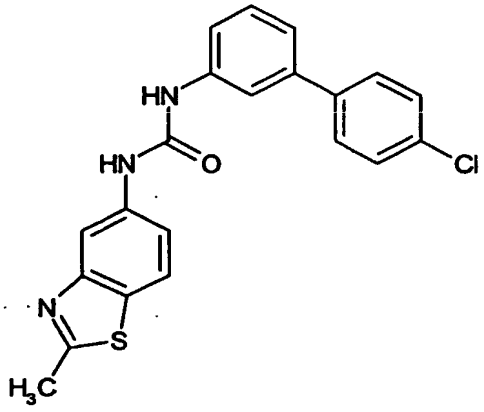
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
30		319,33522	320	243-244	A
31		331,82648	332	230-232	A
32		385,79777	386	240-241	A

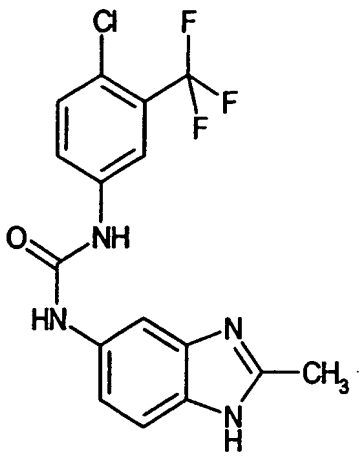
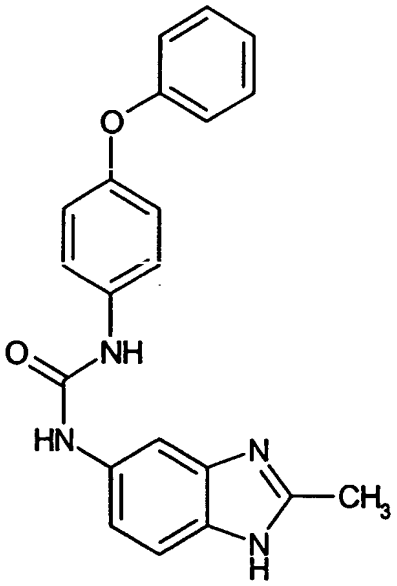
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
33		265,31745	266	237-239	B
34		297,38145	298	198-201	B
35		269,28079	270	239-241	B

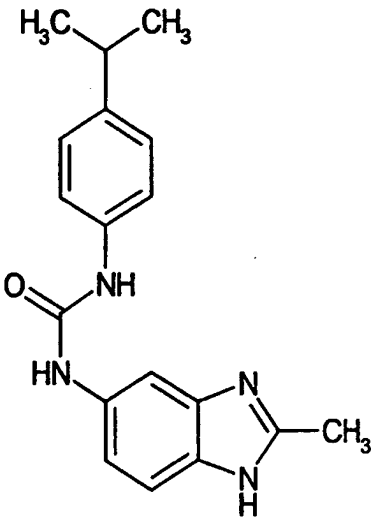
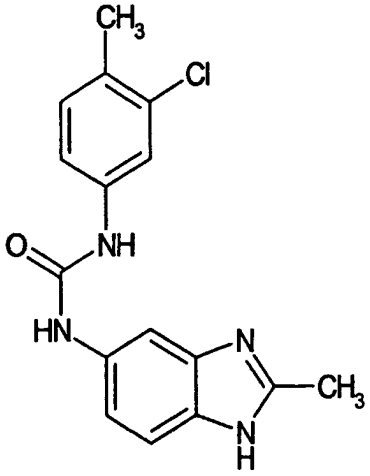
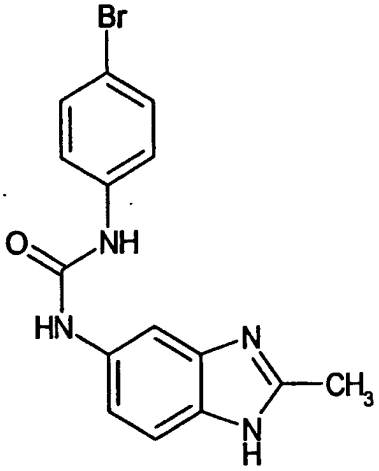
Ex. No	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
36		281,31685	282	219-221	B
37		343,38854	344	212-214	B
38		314,36558	315	219-222	C

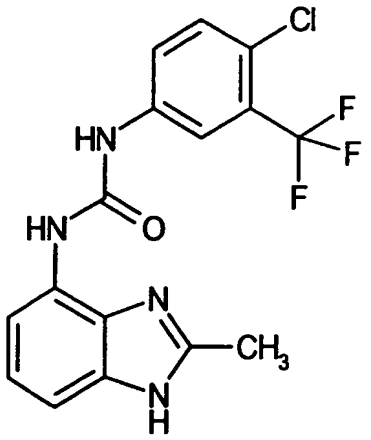
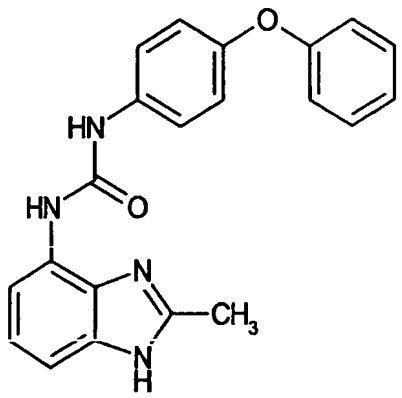
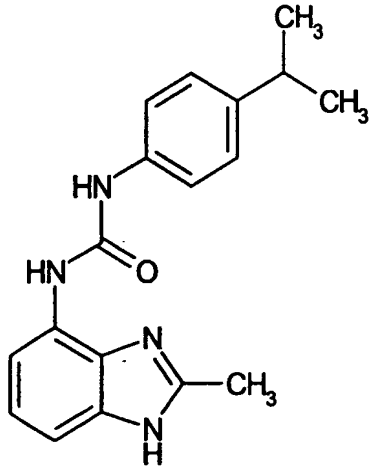
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
39		325,43563	326	208-210	A
40		333,4149	334	>250	A
41		319,28874	320	211-213	A

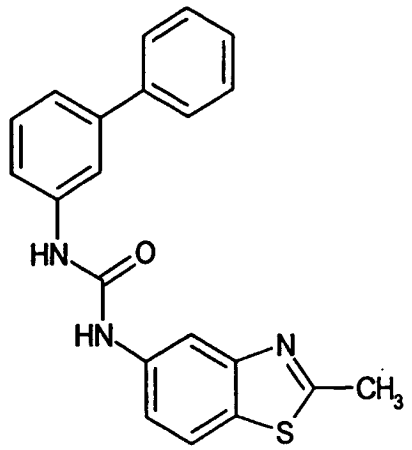
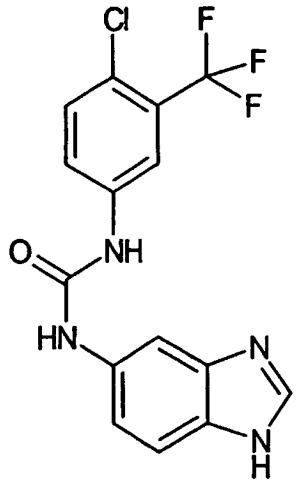
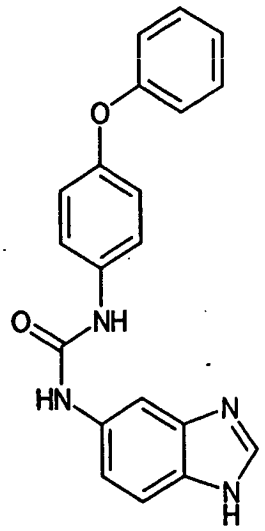
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
42		346,42958	347	212-213	B
43		318,32892	319	242-243	C
44		368,33687	369	>250	B

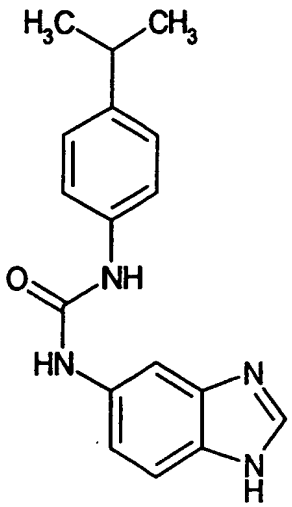
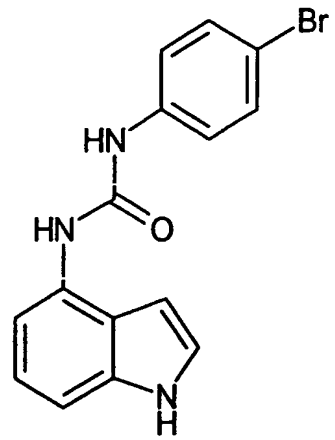
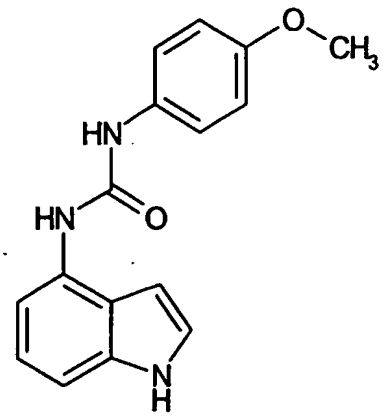
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
45		330,36498	331	206-208	C
46		327,38914	328	204-206	B
47		393,89817			B

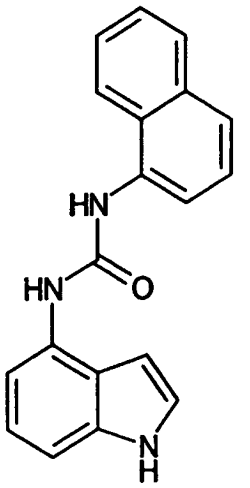
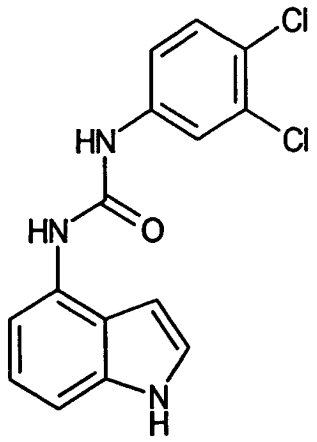
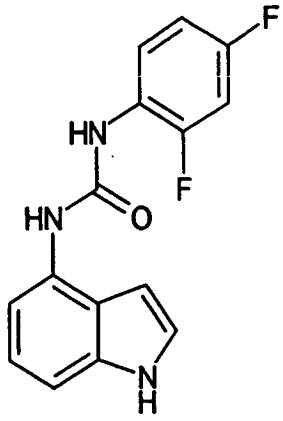
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
48		368,74844	369	162-166	C
49		358,40321	359	243-245	C

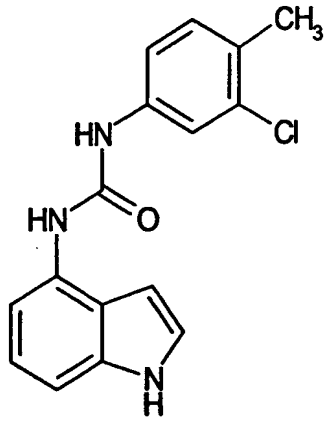
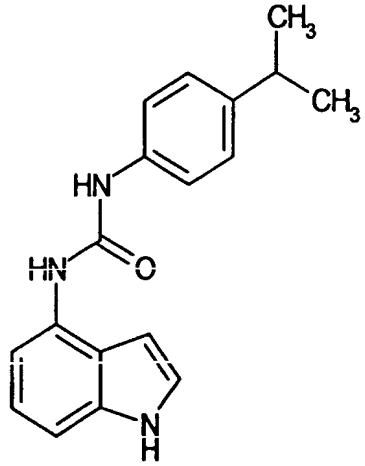
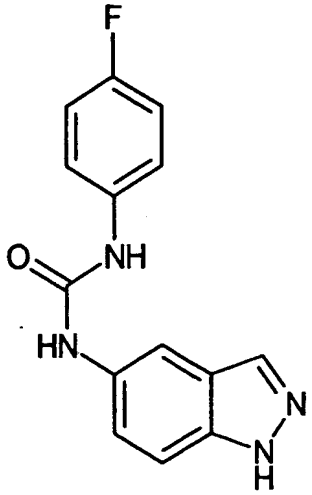
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
50		308,3863	309	>250	C
51		314,77715	315	200-204	C
52		345,20106	347	>250	C

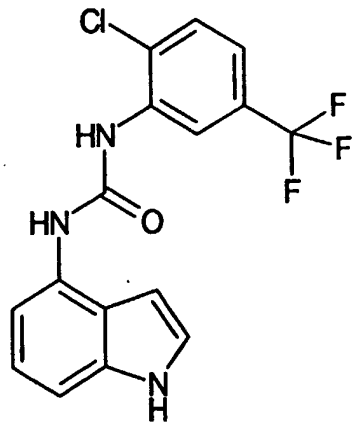
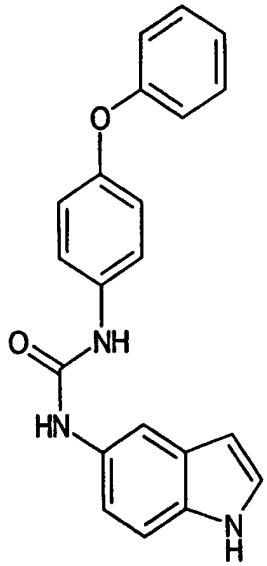
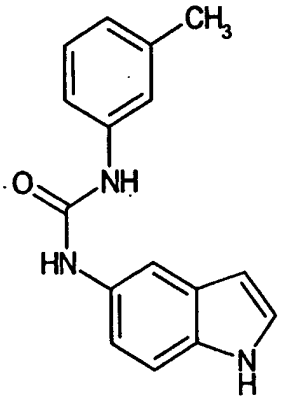
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
53		368,74844	369	189-191	A
54		358,40321	359	223-225	A
55		308,3863	309	216-218	B

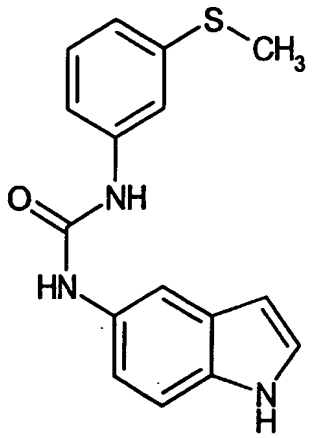
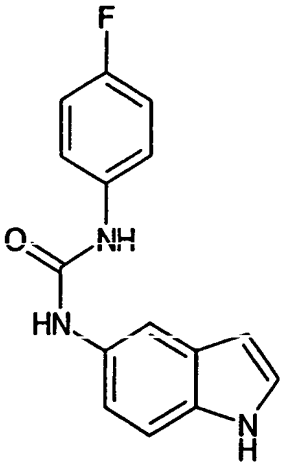
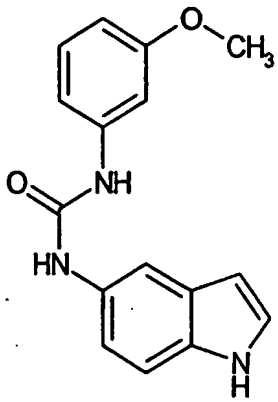
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
56		359,45314	360	216-219	B
57		354,72135	355	218-220	B
58		344,37612	345	235-237	B

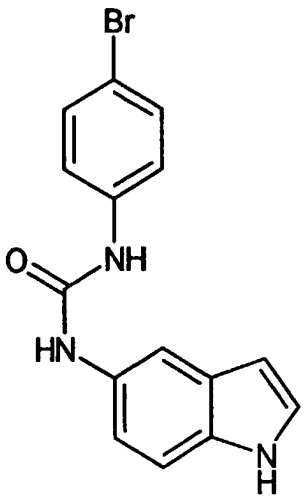
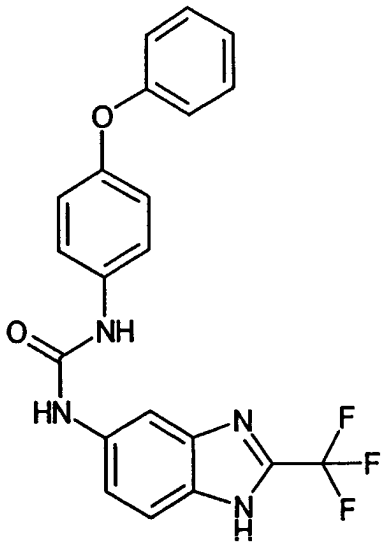
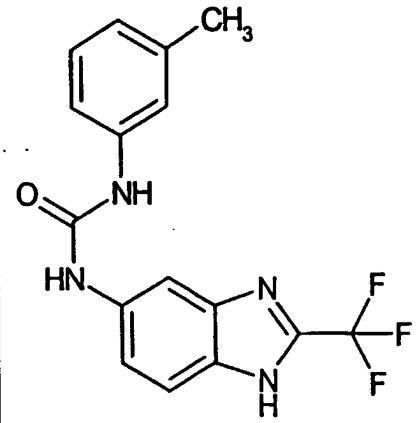
Ex. No	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
59		294,35921	295	226-229	C
60		330,18639	332	238-240	B
61		281,31685	282	230-232	C

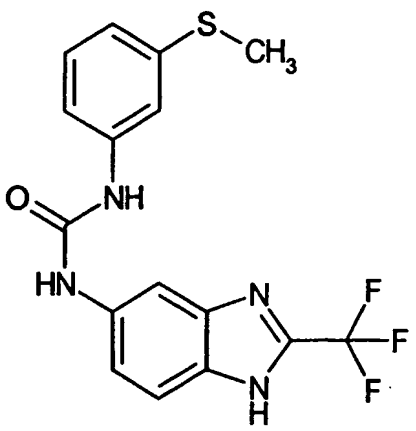
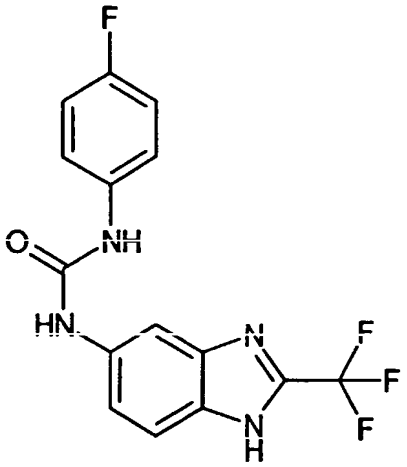
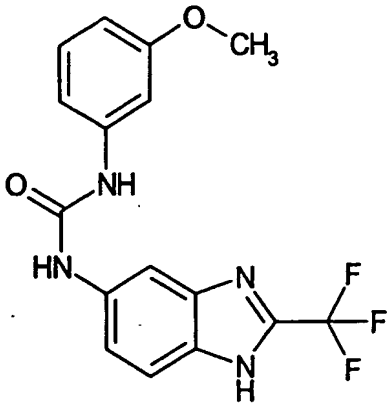
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
62		301,3509	302	>250	A
63		320,18042	320	244-245	A
64		287,27122	288	247-248	C

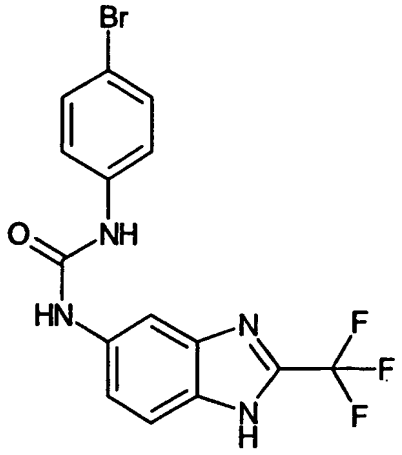
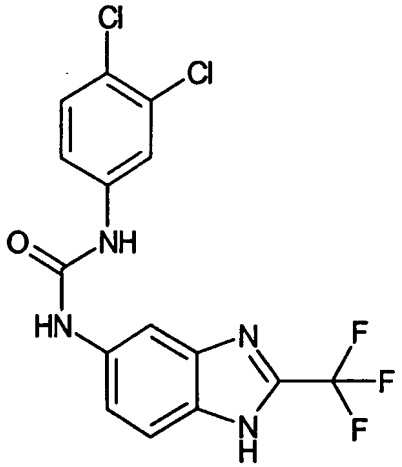
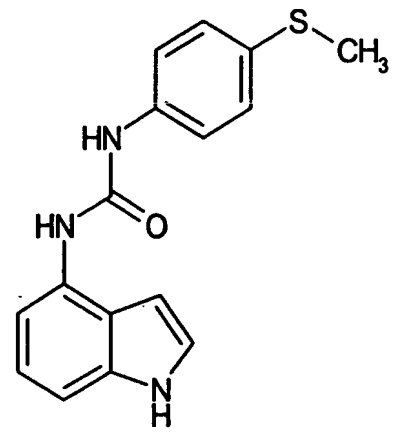
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
65		299,76248	300	246-247	A
66		293,37163	294	222-224	A
67		270,26837	271	>250	C

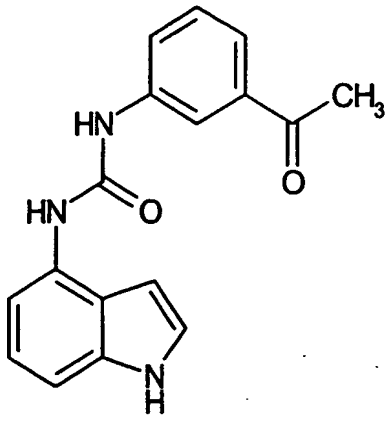
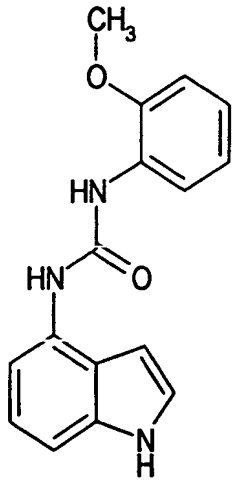
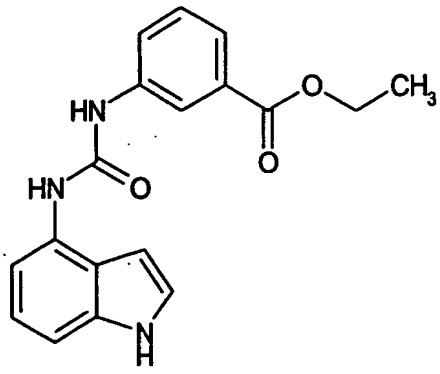
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
68		353,73377		211-213	A
69		343,38854	344	231-233	B
70		265,31745	266	>250	C

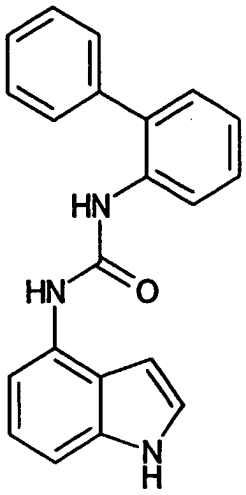
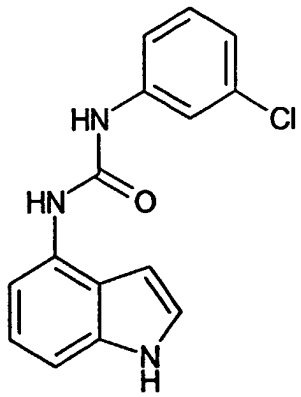
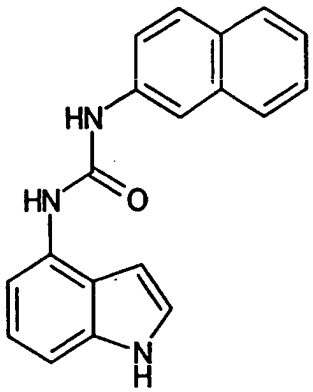
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
71		297,38145	298	236-239	B
72		269,28079	270	243-245	C
73		281,31685	282	227-229	C

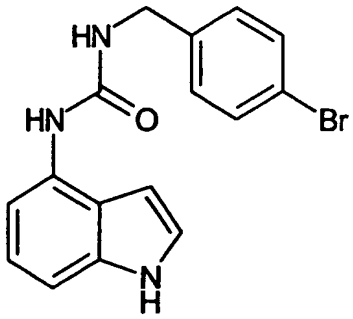
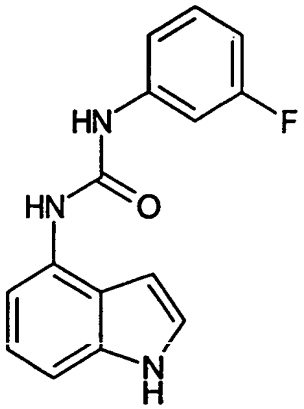
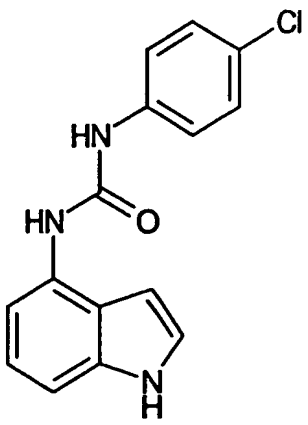
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
74		330,18639	332	>250	C
75		412,3745	413	239-241	C
76		334,30341	335	245-247	C

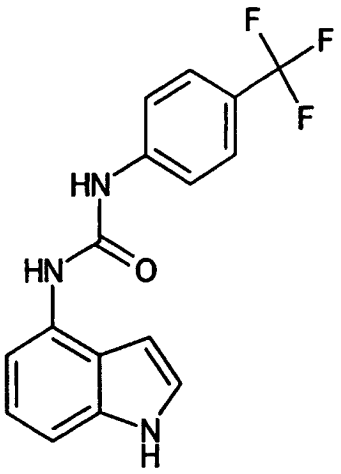
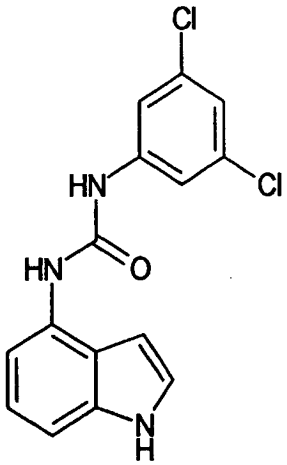
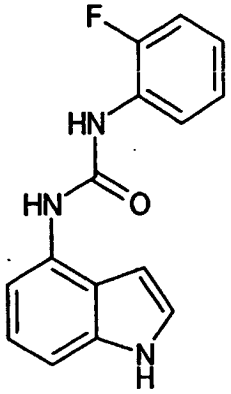
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
77		366,36741	367	226-228	C
78		338,26675	339	242-243	C
79		350,30281	351	233-237	C

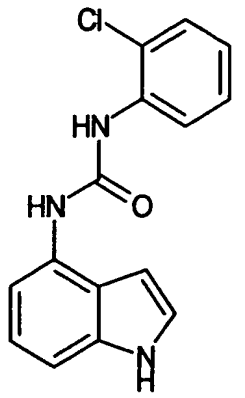
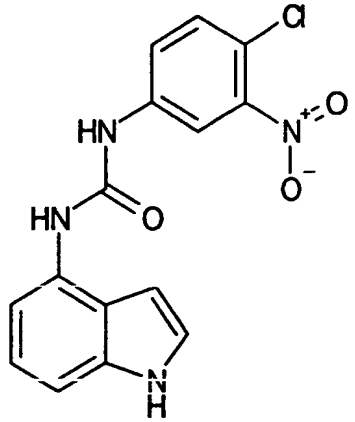
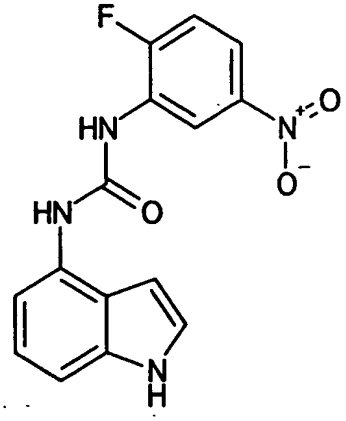
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
80		399,17235	401	>250	C
81		389,16638	389	240-242	C
82		297,38145	298	228-231	C

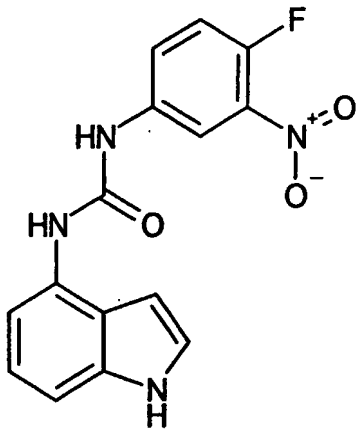
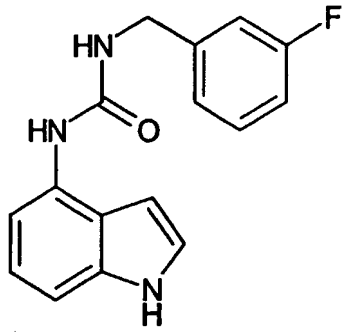
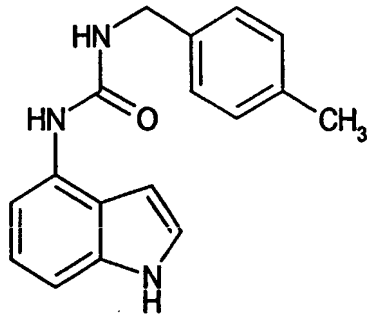
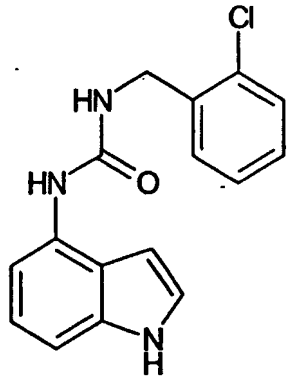
Ex. No	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
83		293,328	294	205-207	C
84		281,31685	282	208-209	C
85		323,35449	324	194-196	A

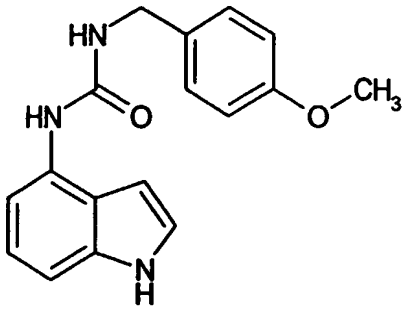
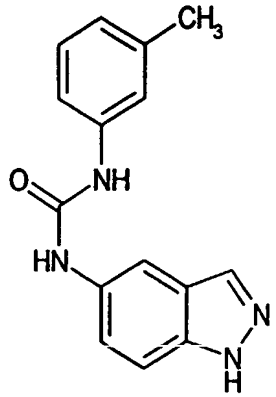
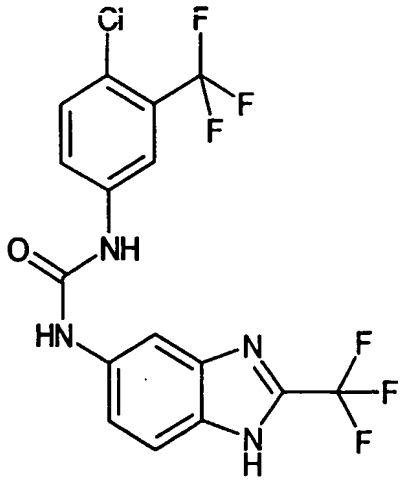
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
86		327,38914	328	104-106	C
87		285,73539	286	238-239	B
88		301,3509	302	242-243	B

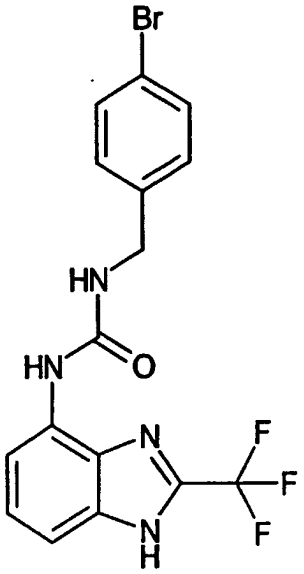
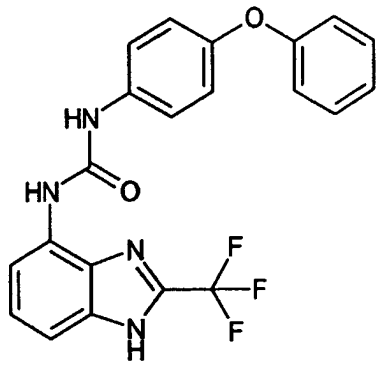
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
89		344,21348	346	199-202	A
90		269,28079	270	225-226	C
91		285,73539	286	247-248	B

Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
92		319,28874	320	242-243	B
93		320,18042	320	262-263	B
94		269,28079	270	244-246	C

Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
95		285,73539	286	244-246	B
96		330,73292	331	233-235	B
97		314,27832	315	261-263	C

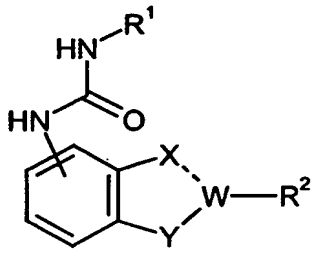
Ex. No.	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
98		314,27832	315	248-251	B
99		283,30788	284	190-192	C
100		279,34454	280	223	B
101		299,76248	300	237-238	B

Ex. No	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
102		295,34394	296	201-202	C
103		266,30503	267	ND	C
104		422,71973	423	ND	C

Ex. No	MOLSTRUCTURE	MW	MS	melting point	hVR1 class
105		413,19944	415	ND	C
106		412,3745	413	ND	B

CLAIMS

(1) A medicament comprising a urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as an active ingredient:



(I)

wherein

R^1 is C_{1-6} alkyl substituted by phenyl or thienyl (in which said phenyl and thienyl are substituted by R^{11}, R^{12}, and R^{13}), C_{3-8} cycloalkyl optionally fused by benzene, thienyl, quinolyl, carbazolyl of which N-H is substituted by N-R^{11}, 1,2-oxazolyl substituted by R^{11}, naphthyl substituted by R^{14} and R^{15}, phenyl substituted by R^{11}, R^{12}, and R^{13}, phenyl fused by C_{4-8} cycloalkyl or saturated or unsaturatd C_{4-8} heterocyclic ring having one or two hetero atoms selected from the group consisting of N, O, S, and SO_2,

wherein said cycloalkyl and heterocyclic ring are optionally substituted by R^{11},

in which

R^{11}, R^{12} and R^{13} are different or identical and represent hydrogen, halogen, oxo, nitro, carboxyl, C_{1-6} alkyl optionally substituted by hydroxy or mono-, di-, or tri- halogen, carbamoyl, C_{1-6} alkyl-carbamoyl, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri-halogen, C_{1-6} alkoxycarbonyl, amino, C_{1-6} alkylamino, di(C_{1-6}

alkyl)amino, morpholino, benzyl, phenoxy, mono-, di-, or tri- halogen substituted phenoxy, C_{1-6} alkylthio, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, C_{1-6} alkyl substituted 4,5-dihydro-1,3-oxazolyl, 1,2,3-thiadiazolyl, phenyl optionally substituted by one to three substituents,

in which the substituents are each different or identical and selected from the group consisting of hydrogen, halogen, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkanoyl, and carboxy,

or

the substituent represented by the formula $-SO_2-N-R^{111}$

wherein

R^{111} represents hydrogen, 5-methyl-isoxazole, or 2,4 dimethylpyrimidine;

R^{14} is hydrogen, hydroxy, or C_{1-6} alkoxy;

R^{15} is hydrogen, hydroxy, or C_{1-6} alkoxy;

X, Y, and W are different or identical represent C, CH, CH_2, C(O), N, NH, S, O, SO or SO_2;

the dashed line between X and W represents a single bond or a double bond;

R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, mercapto, trifluoromethyl, and methylthio,

or

is absent;

with the proviso that

if the bond between X--W is a double,

X is N or CH;

W is N or C; and

Y is selected from the group consisting of NH, S, O, CH_2, SO, and SO_2;

with the proviso that when W is N,R^2 is absent;

if the bond between X--W is a single,

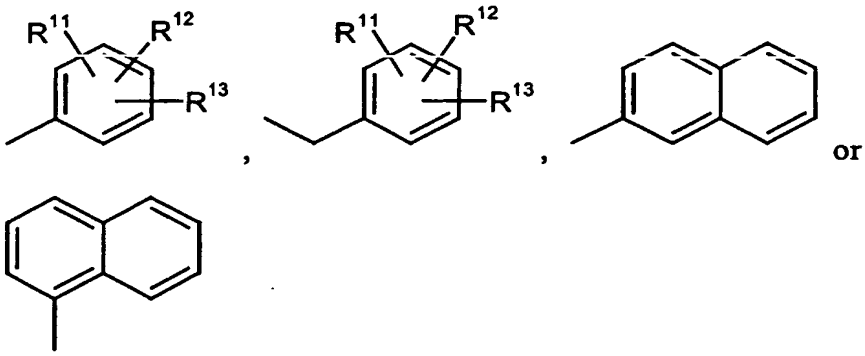
X and Y independently represent CH_2, CO, NH, S, O, SO, or SO_2;

W is N, CH, S, O, SO or SO_2;

with the proviso that when W is S, O, SO or SO_2, R^2 is absent.

(2) The medicament comprising a urea derivative of the formula (I), as claimed in claim 1, wherein

R^1 is



wherein

R^{11}, R^{12}, and R^{13} are different or identical and represent hydrogen, halogen, nitro, carboxyl, C_{1-6} alkyl optionally substituted by hydroxy or mono-, di-, or tri- halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri- halogen, C_{1-6} alkoxycarbonyl, carbamoyl, C_{1-6} alkylcarbamoyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, morpholino, phenyl, benzyl, phenoxy, mono-, di-, or tri- halogen substituted phenoxy, mono-, di-, or

tri- halogen substituted phenyl, C_{1-6} alkylthio, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, or the substituent represented by the formula $-SO_2-N-R^{111}$

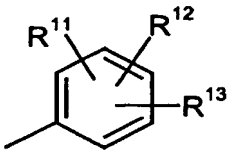
wherein

R^{111} is hydrogen, 5-methyl-isoxazole, or 2,4-dimethyl-pyrimidine.

(3) A medicament comprising a urea derivative of the formula (I), as claimed in claim 1,

wherein

R^1 is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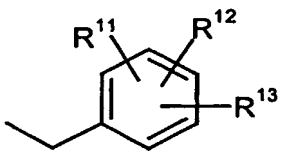
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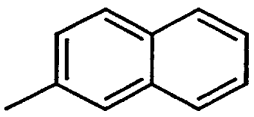
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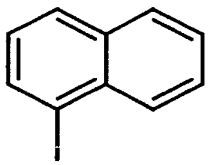
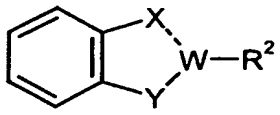


wherein

R^{11}, R^{12}, and R^{13} are different or identical and represent hydrogen, fluoro, chloro, bromo, methyl, isopropyl, methoxy, nitro, ethoxycarbonyl, phenyl, phenoxy, 4-chlorophenyl, methylthio, acetyl, or trifluoromethyl.

(4) A medicament comprising a urea derivative of the formula (I), as claimed in claim 1,

wherein



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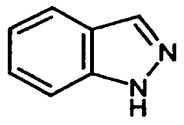
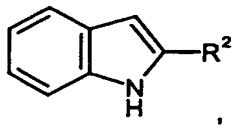
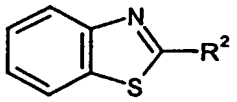
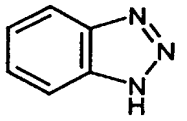
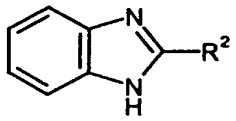
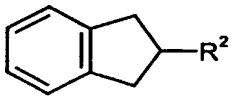
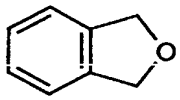
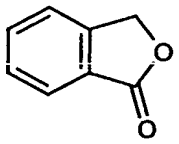
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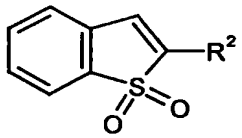

wherein

R^2 is hydrogen, methyl, hydroxy, mercapto, trifluoromethyl, or methylthio.

(5) A medicament comprising a urea derivative of the formula (I), as claimed in claim 1,

wherein

R^2 is hydrogen, methyl, trifluoromethyl, or methylthio.

(6) The medicament as claimed in claim 1, wherein said urea derivative of the formula (I) its tautomeric or stereoisomeric form, or a salt thereof is selected from the group consisting of:

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(1H-indazol-5-yl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(1H-indol-7-yl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(1H-indol-4-yl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-[2-(trifluoromethyl)-1H-benzimidazol-4-yl]urea;

N-(4-bromobenzyl)-N'-(1H-indol-7-yl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(1,1-dioxido-1-benzothien-6-yl)urea;

N-(1,3-benzothiazol-6-yl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;

N-(2-methyl-1,3-benzothiazol-5-yl)-N'-(3-methylphenyl)urea;

N-(4-fluorophenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;

N-(2-methyl-1,3-benzothiazol-5-yl)-N'-[3-(trifluoromethyl)phenyl]urea;

N-(2-methyl-1,3-benzothiazol-5-yl)-N'-(4-phenoxyphenyl)urea;

N-(4-bromophenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;

N-(2-methyl-1,3-benzothiazol-5-yl)-N'-(2-naphthyl)urea;

N-(3,4-dichlorophenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;

N-(2,4-difluorophenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;

N-(3-chloro-4-methylphenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;

N-[2-chloro-5-(trifluoromethyl)phenyl]-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;

N-(4-isopropylphenyl)-N'-(2-methyl-1,3-benzothiazol-5-yl)urea;

N-(2-methyl-1,3-benzothiazol-5-yl)-N'-(1-naphthyl)urea;

N-(1H-indol-4-yl)-N'-[3-(trifluoromethyl)phenyl]urea;

N-(1,1'-biphenyl-3-yl)-N'-(1H-indol-4-yl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(2-methyl-1H-benzimidazol-4-yl)urea;

N-(2-methyl-1H-benzimidazol-4-yl)-N'-(4-phenoxyphenyl)urea;

N-(1H-indol-4-yl)-N'-(1-naphthyl)urea;

N-(3,4-dichlorophenyl)-N'-(1H-indol-4-yl)urea;

N-(3-chloro-4-methylphenyl)-N'-(1H-indol-4-yl)urea;

N-(1H-indol-4-yl)-N'-(4-isopropylphenyl)urea;
N-(4-fluorophenyl)-N'-(1H-indazol-5-yl)urea;
N-[2-chloro-5-(trifluoromethyl)phenyl]-N'-(1H-indol-4-yl)urea;
ethyl 3-{[(1H-indol-4-ylamino)carbonyl]amino}benzoate;
and
N-(4-bromobenzyl)-N'-(1H-indol-4-yl)urea.

(7) The medicament as claimed in claim 1 further comprising one or more pharmaceutically acceptable excipients.

(8) The medicament as claimed in claim 1, wherein said urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof is a VR1 antagonist.

(9) The medicament as claimed in claim 1, wherein said urea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof is effective for treating or preventing a disease selected from the group consisting of urge urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and inflammatory disorders.

(10) A method for treating or preventing disorder or disease associated with VR1 activity in a human or animal subject, comprising administering to said subject a therapeutically effective amount of the medicament as claimed in claim 1.

(11) The method of claim 10, wherein said disorder or disease is a urological disorder or disease.

(12) The method of claim 10, wherein said disorder or disease is selected from the group consisting of urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and inflammatory disorders.

(13) The method of claim 10, wherein said urea derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is administered with one or more pharmaceutically acceptable excipients.

(14) Process for controlling urological disorders in humans and animals by administration of a VR1-antagonisticly effective amount of at least one compound according to any of Claims 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/14215

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/428 A61K31/416 A61K31/4184 A61K31/4192 A61K31/365
A61K31/404 C07D277/72 C07D277/62 C07D277/74 C07D277/64
C07D209/08 C07D231/56 C07D249/18 C07D235/06 C07D333/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 1 256 574 A (KIRIN BREWERY) 13 November 2002 (2002-11-13) see whole document, especialy examples 13,20,67-70,72,73,76,78,79,84,85-91,100-11 3	1-5,7,9
X	& WO 01 56988 A (KIRIN BEER) 9 August 2001 (2001-08-09) ---	1-5,7,9
X	US 3 711 610 A (KIRCHNER F) 16 January 1973 (1973-01-16) see claim 3 and examples and general formula ---	1-5
X	WO 99 00357 A (VERTEX PHARMA) 7 January 1999 (1999-01-07) see general formula and examples 40,,74,75,81,82,80,86,130 --- -/--	1-5,7,9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2003	14/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/14215

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D307/88

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 75106 A (WISCONSIN ALUMNI RES FOUND) 14 December 2000 (2000-12-14) cited in the application the whole document	1-14
Y	WO 01 68652 A (BOEHRINGER INGELHEIM INT ;NOVO NORDISK AS (DK)) 20 September 2001 (2001-09-20) see claim 55,33 and whole document	1-14
P,Y	WO 02 090326 A (RAMI HARSHAD KANTILAL ;WYMAN PAUL ADRIAN (GB); THOMPSON MERVYN (GB) 14 November 2002 (2002-11-14) the whole document	1-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat[redacted] Application No
PCT/EP 02/14215

C:(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 02 16318 A (JEONG YEON SU ;JOO YUNG HYUP (KR); KIM HEE DOO (KR); KIM SUN YOUNG) 28 February 2002 (2002-02-28) see defintions of R8 and examples 2,114,116,128 and 129	1-14

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5,7-14(partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the examples, and claim 4 when dependent on claim 2, i.e. wherien the heterocycle is defined as in claim 4 and the group R1 is as defined in claim 2.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/14215

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-5,7-14(partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/14215

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